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RELATION OF FILTRABLE VIRUSES TO DISEASES OF THE NERVOUS SYSTEM

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NEW YORK

Filtrable viruses have been attracting the attention of an increasing number of pathologists, bacteriologists and immunologists in the last few years. Inasmuch as many of these incitants of disease manifest themselves by activities in the nervous system, neurologists, psychiatrists and neuropathologists have also become interested in them. To the latter group of workers these active agents should be particularly intriguing, because by means of them excellent opportunities for experimental investigation of the effects of diseases on the nervous system are afforded. In the past, however, much of this work has been conducted by men relatively unfamiliar with the nervous system and the methods of its study. As a result, erroneous and conflicting reports concerning virus disorders of the brain, cord and nerves have appeared. In order to correct these mistakes and to end the confusion, either workers in the virus field must become neuropathologists or neuropathologists must learn more about viruses, their activities in susceptible hosts and the immunologic responses excited by them. I am neither familiar with all of the viruses nor a thoroughly trained neuropathologist and hence am unqualified to dissipate much of the existing confusion. Consequently, at this time, I shall attempt only a statement of a few of the difficulties encountered by workers in this field and an enumeration and evaluation of some of the conflicting opinions regarding viruses and their relation to diseases of the nervous system.

NATURE OF VIRUSES

A few remarks concerning the nature [1] of the filtrable viruses themselves may serve to emphasize at this time the difficulties that will be encountered in a discussion of their relation to diseases of the nervous system. The term filtrable virus literally means a noxious agent or poison susceptible of being passed through a filter. By usage it came to indicate certain disease-inciting agents capable of passing through

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1. For a detailed discussion of the nature of these active agents see Rivers, T. M.: Nature of Viruses, Physiol. Rev., to be published.

diatomaceous earth and kaolin filters impervious to ordinary bacteria. After a time, however, some minute bacteria and spirochetes were observed to be capable also of penetrating such filters, and not a few diseases, e. g., yellows of asters, herpes zoster and rabies, because of their characteristics, have been placed in the filtrable virus group, even though their incitants have not been shown to be filtrable or have been found to pass filters with great difficulty. Moreover, it has been recently demonstrated that filters of calcined gypsum (plaster of paris) allow the passage of ordinary bacteria while restraining the filtrable viruses. Under these conditions the order of affairs is reversed. Thus, the term filtrable viruses may be misleading and confusing. Yet by general consent it now designates a group of active transmissible agents that produce a large number of diseases attacking individuals in practically every realm of plant and animal life, e. g., bacteriophagy, mosaic disease of plants, polyhedral diseases of insects, canine distemper, louping ill, cowpox and foot and mouth disease of cattle, Borna disease and pernicious anemia of horses, fowl plague, Rous sarcoma of chickens, herpes febrilis or fever blisters, yellow fever, measles, smallpox, rabies and acute anterior poliomyelitis.

Since many of these diseases are exceedingly common, one naturally asks the question: Wherein are they so peculiar that their incitants must be referred to in a noncommittal way as filtrable viruses? As some of the maladies produced by these incitants are highly contagious, most workers have thought of the causative agents as small bacteria, spirochetes or protozoa. Yet no one has conclusively shown that they are capable of multiplication in a medium devoid of living susceptible host cells. Hence, they appear to be obligate parasites, or in some way to be associated more intimately with host cells than are ordinary pathogenic bacteria. Furthermore, in spite of the excellent work on the elementary bodies of fowl pox and vaccinia conducted by Borrel, Paschen, Goodpasture and Ledingham, doubt still exists regarding the visibility of the incitants of these diseases, and also there are indications that at least some of the viruses are of such small size as to preclude the possibility of an estimation of their magnitude by means of optical instruments. Indeed, Beijerinck has spoken of the etiologic agent of tobacco mosaic as a *contagium vivum fluidum*. Moreover, some investigators have expressed the belief that certain viruses are inanimate. For example, Woods, in 1899, asserted that the causal agent of tobacco mosaic is an oxidizing enzyme, and Vinson now holds that it is an inanimate chemical substance. Högyes expressed the opinion that the incitant of rabies is an enzyme or, "alternatively, that the tissues themselves might spontaneously become virulent as the result of changes in their chemical composition." At one time Remlinger said: "The rabies virus, which is at once filterable, diffusible and capable of reproducing

the disease from case to case, appears to occupy a place midway between the microbes and diastases." Sanfelice, in 1914, reported that the incitant of fowlpox is an inanimate poison, nucleoprotein in character and capable of injuring normal cells in such a manner that they elaborate a poison of a similar nature, which in turn attacks other normal cells. Thus, a hypothesis was presented to explain how in the case of an inanimate substance reproduction in series may occur. Similar hypotheses regarding the nature of the agents causing bacteriophagy, Rous sarcoma, and herpes febrilis have been proposed by a number of workers in recent years, and Murphy has given to this hypothetic type of disease-inciting agent the name transmissible mutagens.

For a long time, certain investigators have contended that the incitants of measles, influenza, poliomyelitis,[2] epidemic encephalitis[3] and fox encephalitis are varieties of green streptococci. Now that attention is being focused on bacterial dissociation and filtrable forms of bacteria, workers fostering the cause of streptococci state that the etiologic agents of these diseases[4] are merely filtrable noncultivable forms of these well known organisms. Without unnecessarily prolonging the discussion, it can be stated that neither ordinary bacteria nor their filtrable forms have been conclusively demonstrated to be the cause of any of the virus maladies.

Conflicting ideas and reports concerning the nature of viruses are bewildering. Yet in regard to these agents two facts are gradually being established, namely, that they are small and that none of them has been definitely shown capable of growth on lifeless mediums. Because of their minute size and their inability to regenerate in the absence of living cells, one would be unaware of their existence were

2. Rosenow, E. C.: Report on the Treatment of Fifty-Eight Cases of Epidemic Poliomyelitis with Immune Horse Serum, J. Infect. Dis. **22**:379 (April) 1918. Rosenow, E. C.; Towne, E. B., and von Hess, C. L.: The Elective Localization of Streptococci from Epidemic Poliomyelitis, J. Infect. Dis. **22**:313 (April) 1918. Rosenow, E. C., and Wheeler, G. W.: The Etiology of Epidemic Poliomyelitis, J. Infect. Dis. **22**:281 (April) 1918.

3. (*a*) Amoss, H. L.: Immunological Distinctions of Encephalitis and Poliomyelitis, J. Exper. Med. **33**:187, 1921. (*b*) Rosenow, E. C.: The Production of Spasms of the Diaphragm in Animals with a Streptococcus from Epidemic Hiccup, J. Infect. Dis. **32**:41 (Jan.) 1923; (*c*) Changes in Streptococcus from Encephalitis, Induced Experimentally, and Their Significance in Pathogenesis of Epidemic Encephalitis and Influenza, ibid. **33**:531 (Dec.) 1923; (*d*) Streptococci in Relation to Etiology of Epidemic Encephalitis: Experimental Results in Eighty-One Cases, ibid. **34**:329 (April) 1924. (*e*) Rosenow, E. C., and Jackson, G. H., Jr.: Microscopic Demonstration of Bacteria in the Lesions of Epidemic (Lethargic) Encephalitis, ibid. **32**:144 (Feb.) 1923.

4. Rosenow, E. C.: The Relation of Streptococci to the Filtrable Virus of Epizootic Encephalitis of the Fox, J. Infect. Dis. **48**:304 (March) 1931.

it not for the results of their activities as exhibited in susceptible hosts.[5] Consequently, a study of viruses must, for the moment at least, consist of observations of the results of these activities in natural and experimental hosts, in the tissues of hosts, in emulsions and filtrates of the tissues or in tissue cultures. Therefore, persons seriously interested in viruses should become clinicians and pathologists as well as bacteriologists and immunologists.

The confused state of knowledge of the viruses at the present time makes it exceedingly difficult to define the nature of these active agents. The easiest way out of the dilemma, however, would be the acceptance of the presumptive evidence that viruses are minute organisms. Yet the easiest way and the one that best fits the experiences of the day may not be the right one. Furthermore, excessive skepticism and the habit of too readily accepting presumptive evidence are equally productive of sterility. Unless viruses represent an unknown form of life, proof of their living nature would not be a striking discovery. If, however, some of them are not animate, absolute proof of such a fact would be of fundamental biologic importance. Therefore, care should be exercised that immoderate skepticism, on the one hand, and mental security offered by presumptive evidence, on the other, do not dull efforts to obtain a better understanding of the viruses, some of which may be minute organisms, while others may represent unfamiliar forms of life, and still others may be inanimate transmissible incitants of disease.

Although the nature of the viruses is still an open question, there is little doubt about what they can do or about the importance of their activities. Therefore, without further comment on their nature, one may examine the results of some of their activities, e. g., certain diseases of the nervous system.

ENUMERATION AND GROUPING OF THE DISEASES UNDER DISCUSSION

To facilitate an intelligible discussion of the diseases under consideration, it is essential that they be enumerated and grouped. A tabulation enables one to treat the maladies either collectively or individually. It is fully realized, however, that adequate data regarding many of the diseases preclude the possibility of a final classification being presented at this time.

Encephalitis, myelitis, poliomyelitis, polioencephalitis, polioencephalomyelitis, meningo-encephalitis, meningo-encephalomyelitis and acute disseminated encephalomyelitis are terms frequently encountered

5. Rivers, T. M.: Some General Aspects of Pathological Conditions Caused by Filterable Viruses, Am. J. Path. **4**:91, 1928; Viruses, J. A. M. A. **92**:1147 (April 6) 1929.

in the literature dealing with virus diseases. In fact, the predominant, if not the only symptoms and signs of many maladies occurring under natural conditions are attributable to a direct injury of the nervous system induced by the activity of viruses. Such is the case in rabies, acute anterior poliomyelitis, Australian-X disease, epidemic encephalitis, Borna disease, louping ill, and guinea-pig paralysis (table,

Tentative Classification of the Diseases Under Discussion

A. Nervous system predominantly involved	
1. Rabies	Gray matter chiefly involved
2. Acute anterior poliomyelitis	
3. Australian-X disease	
4. Epidemic encephalitis	
5. Borna disease	
6. Louping ill	
7. Guinea-pig paralysis	
B. Involvement of nervous system only a part of pathologic picture	
1. Fowl plague	White and gray matter about equally involved
2. Hog cholera	
3. Canine distemper	
4. Fox encephalitis	
5. Fowl paralysis	
6. Herpes zoster	
7. Mumps	
C. Nervous system experimentally infected	
1. Vaccinia	Pronounced meningeal involvement
2. Psittacosis	
3. Salivary gland disease of guinea-pigs	
4. Herpes febrilis	
5. Yellow fever	
6. Virus III infection in rabbits	
D. Nervous system involved during convalescence ("postinfection encephalitis" with perivascular demyelinization)	
1. Vaccinia	Both white and gray matter involved, but perivascular demyelinization is the striking feature of the pathologic picture
2. Smallpox	
3. Measles	
4. Varicella	
5. Influenza	
6. Canine distemper	
7. Antirabic inoculations	
8. Cases without obvious preceding infection	
E. Demyelinizing diseases with pathologic pictures somewhat similar to those observed in group D	
1. Acute multiple sclerosis	White matter chiefly involved; demyelinization a prominent part of the picture
2. Multiple sclerosis	
3. Schilder's disease	
F. Miscellaneous group	
1. Toxic encephalitis	
2. Recently described encephalitides, *e. g.*, the cases reported by Brown and Symmers	

group A). There are other maladies, for example, fowl plague, hog cholera, canine distemper, fox encephalitis, fowl paralysis, herpes zoster and mumps (table, group B), in which the involvement of the nervous system—the frequency of such an occurrence varies with the disease—is only a part of the pathologic picture. There are still other virus diseases, for instance, herpes febrilis, vaccinia, yellow fever, virus III infections in rabbits, salivary gland disease of guinea-pigs and psittacosis (table, group C), the incitants of which under natural conditions do not usually involve the nervous system. Yet these agents under

experimental conditions are highly injurious to nervous tissue and most of them are capable of propagation in the brains of susceptible hosts. In the course of, or during convalescence from, certain virus diseases, namely, vaccinia, smallpox, measles, varicella, influenza, canine distemper and antirabic inoculations (table, group D), signs and symptoms referable to the central nervous system develop in a very small percentage of cases. In these cases the cerebrospinal injury occurs as a rare complication of exceedingly common diseases, and the exact relation of the inciting agents of these maladies to their complications is not known. This set of unusual and interesting nervous conditions, the postinfection encephalitides, about which more will be said later, is often compared with diseases of group E, acute multiple sclerosis, multiple sclerosis and Schilder's disease. Finally, in group F are listed "toxic encephalitis" occurring in many well known infectious diseases, and several other kinds of encephalitis, some recently described, e. g., by Brown and Symmers, which apparently have no definite relation to any recognized infection.

Inadequate information regarding many of the diseases mentioned doubtless has led to errors in their arrangement in the table, and it must be remembered that such a classification is presented merely to initiate and facilitate discussion. Therefore, I shall indicate immediately both the good and bad features of the tabulation.

A casual examination of the table enables one familiar with virus diseases to ascertain the fact that the maladies in the first three groups, with a few exceptions, have been definitely shown to be caused by viruses, while none of those in the last three groups has been conclusively demonstrated to be induced by the direct action of such agents. Furthermore, in some respects group A, D and E are relatively homogeneous. For instance, the most significant pathologic lesion observed in diseases of group A is nerve cell destruction situated in the gray matter of the brain and cord, while that of maladies in groups D and E consists of demyelinization, chiefly located in the white matter. Moreover, group B is composed of seven diseases, four [6] of which, fowl plague, hog cholera, canine distemper and fox encephalitis, can be grouped according to the distribution of the lesions in the central nervous system, namely, the white and gray matter are about equally involved. Group C, the experimentally induced infections of the brain, however, does not exhibit sufficient homogeneity in the character of the pathologic changes to warrant more than a statement that when-

6. Seifried, O.: Pathologie neurotroper Viruskrankheiten der Haustiere (mit Berücksichtigung der vergleichenden Pathologie), Ergebn. d. allg. Path. u. path. Anat. **24**:554, 1931.

ever the viruses of vaccinia,[7] psittacosis [8] and salivary gland disease [9] of guinea-pigs are inoculated intracerebrally, the involvement of the meninges is more extensive and pronounced than that usually seen in other experimental or natural virus infections of the brain.

Acute Anterior Poliomyelitis.—At one time, acute anterior poliomyelitis would unhesitatingly have been placed in the group of diseases (group A) that involve chiefly the nervous system. Recent epidemiologic studies of Aycock and others,[10] however, revealing a high percentage of persons who, without a history of having had poliomyelitis, possess neutralizing antibodies for poliomyelitic virus have induced many workers to believe it probable that infection with the inciting agent of infantile paralysis may be widespread and that a disease of the brain and cord develops in only a small percentage of those infected. Considerable work on this phase of the problem was done during the last epidemic, and it is hoped that information thus gained will elucidate the subject.

Epidemic Encephalitis.—In spite of the fact that it has not been shown to be a virus disease, epidemic encephalitis has been placed in group A. Vigorous efforts have been made by a number of eminent investigators [11] to demonstrate that the virus of herpes febrilis is the

7. Hurst, E. W., and Fairbrother, R. W.: Experimental Vaccinial Encephalitis in the Monkey and the Rabbit, with Special Reference to the Problem of Encephalitis Following Vaccination in Man, J. Path. & Bact. **33**:463, 1930. Spooner, E. T. C.: A Comparative Histological Study of Acute Meningo-Encephalitis Produced in Rabbits by the Viruses of Neurovaccinia and Herpes Simplex, Am. J. Path. **6**:767, 1930.

8. Rivers, T. M., and Berry, G. P.: Psittacosis: II. Experimentally Induced Infections in Mice, J. Exper. Med. **54**:105, 1931; III. Experimentally Induced Infections in Rabbits and Guinea Pigs, ibid. **54**:119, 1931.

9. Cole, R., and Kuttner, A. G.: A Filterable Virus Present in the Submaxillary Glands of Guinea Pigs, J. Exper. Med. **44**:855, 1926.

10. Aycock, W. L., and Kramer, S. D.: Immunity to Poliomyelitis in Normal Individuals in Urban and Rural Communities as Indicated by the Neutralization Test, J. Prev. Med. **4**:189, 1930; Immunity to Poliomyelitis in a Southern Population as Shown by the Neutralization Test, ibid. **4**:201, 1930. Fairbrother, R. W., and Brown, W. G. S.: The Action of the Serum of Normal Individuals on the Virus of Poliomyelitis, Lancet **2**:895, 1930.

11. (*a*) Doerr, R., and Berger, E.: Herpes Zoster und Encephalitis (mit Einschluss der Encephalitis postvaccinalis), in Kolle, Kraus and Uhlenhuth: Handbuch der pathogenen Mikroorganismen, ed. 3, Jena, Gustav Fischer, 1930, vol. 8, p. 1415. (*b*) Levaditi, C.: Etiology of Epidemic Encephalitis: Its Relation to Herpes, Epidemic Poliomyelitis and Postvaccinal Encephalopathy, Arch. Neurol. & Psychiat. **22**:767 (Oct.) 1929. (*c*) Doerr, R., and Zdansky, E.: Kritisches und Experimentelles zur ätiologischen Erforschung des Herpes febrilis und der Encephalitis lethargica, Ztschr. f. Hyg. u. Infectionskr. **102**:1, 1924.

causal agent. In addition to this agent, other viruses [12] and bacteria [13] have been suggested as incitants. An examination of the literature and my own experiences with viruses, however, lead me to believe that one should admit that one does not know the cause of epidemic encephalitis and then seek for it when suitable occasions arise. If such is the state of affairs, one is justified in asking why the malady has been placed in group A. The clinical picture, pathologic changes observed in the brain and epidemiologic studies, by analogy, warrant its classification with virus diseases of the nervous system. In fact, the status of epidemic encephalitis is similar to that of poliomyelitis prior to its transmission to monkeys by Landsteiner, Flexner and others.

Herpes Zoster.—Many investigators believe that certain cases of zoster are caused by a specific virus. Instances, however, of zoster following mechanical or drug injuries to nerves and of zoster occurring in patients with tabes, tuberculosis of the spine and tumors of the cord have led numerous observers to consider that this type of the disease is due not to an infectious agent, but to trophic changes in the skin incident to nerve injury. In spite of the fact that there is only suggestive evidence of the existence of a zoster virus, and regardless of the conditions under which herpes zoster occurs, the character of the lesions observed in the skin has induced a number of workers familiar with virus diseases to entertain the idea that it is caused by some kind of virus.

The question of whether zoster is caused by one or by several viruses naturally arises. The pathologic changes observed in zoster lesions are strikingly familiar to those seen in herpes febrilis and varicella. In fact, the cutaneous lesions of these three diseases cannot be differentiated one from another by means of the microscope. As a group, however, they can be separated from other cutaneous lesions occurring in man. This is made possible by the presence of acidophilic bodies in the nuclei of affected cells. From records [14] of work dealing with the identity of herpes febrilis and herpes zoster it seems unlikely that the etiologic agents concerned in the majority of cases of these two diseases are identical.

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12. McIntosh, J.: Encephalitis Lethargica (Epidemic Encephalitis), in Andrewes, Arkwright and others: A System of Bacteriology in Relation to Medicine, London, His Majesty's Stationery Office, 1930, vol. 7, p. 169. McIntosh, J., and Turnbull, H. M.: The Experimental Transmission of Encephalitis Lethargica to a Monkey, Brit. J. Exper. Path. **1**:89, 1920.

13. Evans, A. C., and Freeman, W.: Studies on the Etiology of Epidemic Encephalitis: I. The Streptococcus, Pub. Health Rep. **41**:1095, 1926. Rosenow (footnote 3 *d*).

14. Cole, R., and Kuttner, A. G.: The Problem of the Etiology of Herpes Zoster, J. Exper. Med. **42**:799, 1925.

It now remains to consider the relation of zoster to chickenpox. A study of the literature dealing with the subject and the fact that an attack of herpes zoster as a rule does not protect against varicella and vice versa seem to indicate that the majority of the cases of the two diseases are not caused by the same virus.[15]

It is not likely that trophic changes incident to nerve injury alone or to drug poisoning alone, e. g., with arsenic, are capable of producing herpes zoster. If such were the case, the disease should be seen more often under these conditions. The fact that viruses tend to localize in irritated tissues may also account for the relation that has been observed to exist between certain cases of herpes zoster and nerve injury due to chemical, physical or disease-producing agents. Whether the virus localizes primarily in ganglia and subsequently travels by way of nerves to the skin or whether the localization is only in the skin, the site being determined by circulatory and other changes incident to the injury of nerves supplying the region, is not definitely known. There is no reason why the primary localization of the virus may not occur in either place. The fact, therefore, that zoster involves both skin and nervous tissue has induced me to place it in group B instead of group A where it would be listed by many workers as an acute posterior poliomyelitis.

Mumps.—During the course of mumps in an occasional patient symptoms and signs referable to the central nervous system develop, and because of these phenomena epidemic parotitis has been placed in group B (table). Objections to such a classification may be made on the grounds that mumps has not definitely been shown to be a virus disease and that the nervous complications of infectious parotitis should be placed in group D with the postinfection encephalitides. The evidence, however, that mumps is caused by a virus is suggestive enough to warrant its inclusion in a discussion of virus disorders. Moreover, the clinical pictures and the findings in the spinal fluid in mumps meningoencephalitis and postinfection encephalitis are sufficiently dissimilar to suggest that the pathologic changes giving rise to these diseases are not of the same nature. Unfortunately, little is actually known of the histopathology of mumps, because only a few patients with it have come to autopsy. Consequently, there is no histologic evidence that demyelinization, a salient feature of postinfection encephalitis, occurs in mumps meningo-encephalitis.

Demyelinizing Diseases: Groups D and E.—This includes exceedingly interesting disorders, namely, those in which demyelinization is a

15. Rivers, T. M., and Eldridge, L. A., Jr.: Relation of Varicella to Herpes Zoster: I. Statistical Observations, J. Exper. Med. **49**:899, 1929; Relation of Varicella to Herpes Zoster: II. Clinical and Experimental Observations, ibid. **49**:907, 1929.

prominent feature of the pathologic picture. Group E (table) with its diseases of the nature of multiple sclerosis has long been recognized. Group D, however, made up of the postinfection encephalitides, encephalitis following a variety of inoculation procedures [16] and encephalitis occasionally occurring without obvious antecedent infection,[17] has only relatively recently attracted widespread attention. It is true that an encephalomyelitis following antirabic inoculations has been known since 1887,[18] and that a similar condition following measles was described as early as 1886.[19] Nevertheless, interest was focused on this group of maladies only lately and then because of an unexplained but decided increase in their incidence, particularly following jennerian prophylaxis.[20]

16. (*a*) Marie, Remlinger and Vallée: Reports to the International Rabies Conference, Publications of the League of Nations, Geneva, 1927; Ann. Inst. Pasteur, 1928, vol. 42 (supp.). (*b*) Ministry of Health: Report of Committee on Vaccination, London, His Majesty's Stationery Office, 1928. (*c*) Guillain, G., and Barré, J. A.: Paralysie ascendante aiguë de Landry consécutive à une vaccination antityphoidique, Ann. de méd. **6**:218, 1919. (*d*) Lerond, J.: Syndrome de paralysie ascendante, atteignant la face, après injection de sérum antitétanique; Régression rapide au niveau des membres, lente à la face, Bull. et mém. Soc. méd. d. hôp. de Paris **50**:1695, 1926-1927. (*e*) McCoy, G. W.: Antirabic Vaccine Paralysis: Consideration of Various Vaccines, Pub. Health Rep. **45**:1888, 1930. (*f*) Sittig, O.: Ueber eine besondere Form akuter herdförmiger Destruktion des nervösen Gewebes im Gehirn bei Tuberculose (akute nicht-eitrige Encephalitis), Ztschr. f. d. ges. Neurol. u. Psychiat. **10**:289, 1912.

17. (*a*) Flatau, E.: Sur l'épidémie d'inflammation disséminée du système nerveux en Pologne durant l'année 1928 et sur ses rapports avec l'encéphalite léthargique, les atteintes du système nerveux au cours de certaines maladies infectieuses et les cas aigus de sclérose en plaques, Encéphale **24**:619, 1929. (*b*) Greenfield, J. G.: Acute Disseminated Encephalomyelitis (Westphal) as an Independent Disease and as a Sequel or Complication of Certain Virus Infections (Vaccinia, Variola, Measles, Rabies, etc.), in Andrewes, Arkwright and others: A System of Bacteriology in Relation to Medicine, London, His Majesty's Stationery Office, 1930, vol. 7, p. 133. (*c*) Redlich, E.: Ueber ein gehäuftes Auftreten von Krankheitsfällen mit den Erscheinungen der Encephalomyelitis disseminata, Monatschr. f. Psychiat. u. Neurol. **64**:152, 1927.

18. Remlinger, P.: Accidents paralytiques au cours du traitement antirabique, Ann. Inst. Pasteur **19**:625, 1905.

19. Barlow, T.: On a Case of Early Disseminated Myelitis Occurring in the Exanthem Stage of Measles, and Fatal on the Eleventh Day of That Disease, Brit. M. J **2**:923, 1886; On a Case of Early Disseminated Myelitis Occurring in the Exanthem Stage of Measles and Fatal on the Eleventh Day of That Disease (with Report on the Microscopical Examination of the Spinal Cord, by F. G. Penrose), Med.-Chir. Tr. **70**:77, 1887.

20. (*a*) Bastiaanse, F. S. van B.; Terburgh; Bijl, and Levaditi, C.: Encéphalite consécutive à la vaccination antivariolique, Bull. Acad. de méd., Paris **94**:815, 1925. (*b*) Ministry of Health (footnote 16 *b*). (*c*) Ministry of Health: Further Report of Committee on Vaccination, London, His Majesty's Stationery Office, 1930. (*d*) Turnbull, H. M., and McIntosh, J.: Encephalo-Myelitis Following Vaccination, Brit. J. Exper. Path. **7**:181, 1926.

Numerous reports on the clinical, pathologic and experimental findings in cases of postinfection encephalitis have appeared. A detailed account of these findings seems unnecessary; yet a summary of results and an evaluation of prominent views regarding this condition may be of value. The first significant fact to note is that the nervous disorders occur most frequently late in the course of, or during convalescence from, some virus disease. In view of this fact many workers have been induced to believe that the complicating encephalitides are manifestations in the nervous system of the activity of the viruses producing the primary diseases. Consequently, attempts have been made to recover the viruses, particularly vaccine virus, from the brain and cord in fatal cases. The positive results [20d] have been exceedingly few. Next, it was observed that a similar type of encephalitis follows diseases other than those caused by viruses and at times occurs apparently without antecedent infection. Such confusing observations led to the proposal of a hypothesis [16b] in which it is held that an unknown neurotropic virus activated by many diseases, especially those caused by viruses, is responsible for the encephalitis. Attempts to demonstrate the presence of this unknown virus in the brain in fatal cases have also been unsuccessful. In addition to the concepts already mentioned there is another held by a group of workers, notably Perdrau,[21] that a toxin of unknown origin is the causal agent. Finally, a few investigators [22] are willing to entertain the idea that the pathologic changes in the brain are the results of peculiar allergic responses to infection in certain individuals.

The last concept cited was undoubtedly engendered by the fact that a period of time, approximately comparable to that required for the development of sensitivity to a foreign protein, usually elapses between the onset of the primary infection and the inception of the complicating encephalitis. Moreover, it has been suggested by a few workers [23]

21. (*a*) Perdrau, J. R.: The Histology of Post-Vaccinal Encephalitis, J. Path. & Bact. **31**:17, 1928. (*b*) Perdrau, J. R., and Pugh, L. P.: The Pathology of Disseminated Encephalomyelitis of the Dog (the "Nervous Form of Canine Distemper"), J. Path. & Bact. **33**:79, 1930.

22. (*a*) Cramer, C. D.: Uit kliniek en praktijk. Verschijnselen van het centrale zenuwstelsel na koepokinenting, Geneesk. gids **6**:69, 1928. (*b*) Glanzmann, E.: Die nervösen Komplikationen der Varizellen, Variola und Vakzine, Schweiz. med. Wchnschr. **57**:145, 1927.

23. (*a*) Harvey, W. F., and Acton, H. W.: An Examination into the Degree of Efficacy of Anti-Rabic Treatment, Indian J. M. Research **10**:1020, 1922-1923. (*b*) Koritschoner, R., and Schweinburg, F.: Klinische und experimentelle Beobachtungen über Lähmungen nach Wutschutzimpfung, Ztschr. f. Immunitätsforsch. u. exper. Therap. **42**:217, 1925. (*c*) Marie, Remlinger and Vallée (footnote 16 *a*). (*d*) Schweinburg, F.: Ueber die Ursache der Lahmungen nach Wutschutzimpfungen, Zentralbl. f. Bakt. (Abt. 1) **115**:307, 1929-1930. (*e*) Stuart, G., and Krikorian, K. S.: The Neuro-Paralytic Accidents of Anti-Rabies Treatment, Ann. Trop. Med. **22**:327, 1928.

that the nervous complications of antirabic treatments are due either to toxic substances in the inoculum of brain tissue or to the development of sensitiveness to parenterally introduced cord material. Indeed, reports [24] have appeared in which it was stated that paralyses developed in a small percentage of animals after repeated doses of normal homologous or heterologous brain tissue. Histologic examinations of the brains and cords of the paralyzed animals were so inadequate that considerable doubt exists as to whether demyelinization of the type observed in postinfection encephalitis was actually induced.

Discussions of the postinfection encephalitides have centered around the nervous complications of vaccinia, probably because of the ease with which vaccine virus can be handled experimentally. That the virus of vaccinia has been recovered a few times from the spinal fluids [25] and brains [20d] of persons dying of postvaccinal encephalitis is not a surprising fact, because, contrary to older ideas, vaccinia is a generalized infection.[26] Indeed, virus has been obtained from the brains of intradermally vaccinated animals showing neither clinical nor pathologic signs of involvement of the nervous system. Therefore, the mere finding of virus in the brains of vaccinated persons is not admissible as conclusive evidence that it is the cause of the complicating nervous disorders. The experimental production, however, by means of vaccine virus of a disease comparable to that seen in man might be considered convincing evidence. Most workers,[27] in spite of McIntosh's contentions,[28] believe that this has not been accomplished, and are certain that the direct action of vaccine virus on the nervous system leads to a pathologic picture quite different from that seen in postvaccinal encephalitis, with a marked meningeal reaction and an absence of perivascular demyelinization.

In this connection, Perdrau and Pugh's [21b] observations on canine distemper are interesting and important. Distemper is a systemic infection in which the brain is by no means always involved, but, when it is, the virus recovered from it produces distemper in susceptible hosts. Furthermore, demyelinization is not a feature of the usual

24. Koritschoner and Schweinburg (footnote 23 *b*). Stuart and Krikorian (footnote 23 *e*).

25. Eckstein, A.; Herzberg-Kremmer, H., and Herzberg, K.: Klinisch-experimentelle Untersuchungen über die Vakzinations-enzephalitis, Deutsche med. Wchnschr. **56**:264, 1930.

26. Douglas, S. R.; Smith, W., and Price, L. R. W.: Generalized Vaccinia in Rabbits with Especial Reference to Lesions in the Internal Organs, J. Path. & Bact. **32**:99, 1929.

27. Hurst and Fairbrother (footnote 7). Spooner (footnote 7). Ministry of Health (footnote 20 *c*).

28. McIntosh, J., and Scarff, R. W.: The Reaction of the Central Nervous System to Vaccinia Virus, J. Path. & Bact. **33**:483, 1930.

pathologic picture. In some of Perdrau and Pugh's dogs, however, a disseminated encephalomyelitis with perivascular demyelinization developed during or following distemper, which the observers were unable to associate directly either with distemper virus or with an unknown virus. Consequently, in view of these facts and because of the perivascular distribution of the lesions, they were of the opinion that a toxin reaching the brain by way of the blood stream caused the demyelinization seen in the animals.

Numerous workers [29] have considered demyelinizing diseases, such as multiple sclerosis, degenerative rather than inflammatory processes. Other investigators, including Marie,[30] have long held, on the contrary, that these maladies are due either to single or to combined infections. The fact that acute disseminated encephalomyelitis and postinfection encephalitis show a demyelinization similar to, if not identical with, that seen in acute disseminated sclerosis, has added support to the view that the chronic demyelinizing disease, multiple sclerosis, is produced by an infectious agent. In addition to the circumstantial evidence that the disease is infectious, Chevassut [31] and Purves-Stewart [32] claimed to have cultivated the etiologic agent. These claims are far from being established facts.[33] Nevertheless, a number of eminent investigators, for example, Levaditi [34] and Pette,[35] are at present insistent that all of the demyelinizing diseases under discussion are caused by viruses.

Levaditi,[34] enthusiastically carried away by the idea of cytotropism of viruses, has formulated ingenious hypotheses accounting for two kinds of demyelinization. Being aware of del Río Hortega's [36] belief that oligodendrocytes are of ectodermal origin and normally play a rôle

29. Hassin, G. B.: Studies in the Pathogenesis of Multiple Sclerosis, Arch. Neurol. & Psychiat. **7**:589 (May) 1922.

30. Marie, P.: Lectures on Diseases of the Spinal Cord, London, The New Sydenham Society, 1895, p. 124.

31. Chevassut, K.: The Etiology of Disseminated Sclerosis, Lancet **1**:552, 1930.

32. Purves-Stewart, J.: A Specific Vaccine Treatment in Disseminated Sclerosis, Lancet **1**:560, 1930.

33. Putnam, T. J.; McKenna, J. B., and Morrison, L. R.: Studies in Multiple Sclerosis: I. The Histogenesis of Experimental Sclerotic Plaques and Their Relation to Multiple Sclerosis, J. A. M. A. **97**:1591 (Nov. 28) 1931. Weil, A.: A Study of the Etiology of Multiple Sclerosis, ibid. **97**:1587 (Nov. 28) 1931. Hicks, J. A. B., and Hocking, F. D. M.: Observations on a Spherule Recently Described in Disseminated Sclerosis, Lancet **2**:401, 1931.

34. Levaditi, C.: Les ultravirus provocateurs des ectodermoses neurotropes, Ann. Inst. Pasteur **45**:673, 1930.

35. Pette, H.: Ueber die Pathogenese der multiplen Sklerose, Deutsche Ztschr. f. Nervenh. **105**:76, 1928.

36. del Río Hortega, P.: Tercera aportación al conocimiento morfológico e interpretación funcional de la oligodendroglía, Mem. r. Soc. espań. de hist. nat. **14**:5, 1928.

in the laying down of myelin, he considers the demyelinization occurring in certain maladies, e. g., Schilder's disease, to be due to an oligodendrocytotropic virus that causes an inversion of the oligodendrocytes' metabolism, with the result that myelin is removed from the nerves. In other diseases, such as postvaccinal encephalitis, the destruction of myelin is held to be the result of inflammation and of the lipolytic activity of certain cells, particularly the microglial elements. These are plausible hypotheses, but are not supported by convincing experimental evidence.

Reports in the literature and my own experience with viruses have revealed no authentic instance in which a known virus acting directly on the nervous system has produced demyelinization of the type occurring in diseases of groups D and E (table). In fact, when well recognized viruses, such as those operating in diseases of groups A, B and C (table), attack the brain and cord, demyelinization of the type under discussion is not found. Therefore, if the destruction of myelin is due to the activity of a virus, not only is the agent unknown and different from other viruses, but the disease caused by it has not been experimentally transmitted from one animal to another. These facts do not exclude the possibility that viruses are the cause of demyelinizing disorders, but they should induce one to hesitate before accepting the idea that such agents are the incitants of the peculiar conditions. Furthermore, the indirect action of viruses, toxins, allergic phenomena, vitamin deficiencies, constitutional defects [37] and enzymes [38] are at least worthy of serious consideration in connection with the question of demyelinization.

PATHWAYS OF INFECTION

Having enumerated the disorders of the nervous system that either are or might be associated with the activities of viruses, and having discussed some of them, I shall now pass to a consideration of a few topics of a more general nature, notably, the pathways employed by viruses for obtaining entry into, dissemination through and exit from the nervous system, the peculiarities of the pathologic changes caused by viruses in the brain and cord and, finally, immunity and specific serum therapy.

37. Balyeat, R. M.: The Hereditary Factor in Allergic Diseases with Special Reference to the General Health and Mental Activity of Allergic Patients, Am. J. M. Sc. **176**:332, 1928. Batten, F. E.: Two Cases of a Family Disease, the Symptoms of Which Closely Resemble Disseminated Sclerosis, Proc. Roy. Soc. Med. (Sect. Neurol.) **2**:35, 1908-1909. Liepelt, A.: Ueber familiäre Spinalerkrankung bei familiärer Biermer'scher Anämie, Deutsche Ztschr. f. Nervenh. **90**:201, 1926.

38. Crandall, L. A., Jr., and Cherry, I. S.: Presence of an Olive Oil Splitting Lipase in the Blood of Patients with Multiple Sclerosis, Proc. Soc. Exper. Biol. & Med. **28**:572, 1931.

Portals of Entry.—The most obvious possible portals of entry of viruses into the central nervous system are: (1) by way of the blood stream, (2) by means of the perineural spaces, (3) by direct extension along nerves, accomplished by the propagation of the active agents through the cells of the neurilemma, and (4) by way of axis-cylinders of nerves within which the incitants grow until the bodies of the cells themselves are reached. A consideration of these portals of entry reveals no reason to believe that only one of them is used by viruses.

Experimental evidence regarding the manner in which viruses reach the nervous system is incomplete, and much of it deals with the anatomic relation of the brain and subarachnoid space to the blood vessels and lymphatics of the nose and pharynx. Indeed, the possibility that the lymphatics of the nasal mucous membranes may be directly connected with the olfactory perineural spaces, which in turn are continuous with the subarachnoid space, has caused considerable discussion. Clark's [39] recent work, however, seems to show that a direct connection between them does not exist. Nevertheless, this worker has demonstrated that particles of the magnitude of infectious agents can obtain immediate entrance into the perineural spaces of the olfactory nerves and thus quickly reach the surface of the brain.

The route described by Clark is undoubtedly one way by which viruses may enter the brain. It seems advisable, however, to study the subject further before accepting it as the one along which a large number of these incitants of nervous disorder actually travel. For instance, most of the experimental work conducted with herpetic [40] and rabic [41] viruses appears to indicate that these agents reach the brain not by perineural spaces but by growth along axis-cylinders of nerves. Furthermore, the distribution of lesions and the type of involvement of the blood vessels indicate that certain viruses, for example, those

39. Clark, W. E. le Gros: Anatomical Investigation into the Routes by Which Infections May Pass from the Nasal Cavities into the Brain, Ministry of Health, Reports on Public Health and Medical Subjects, no. 54, London, His Majesty's Stationery Office, 1929.

40. Goodpasture, E. W.: The Axis-Cylinders of Peripheral Nerves as Portals of Entry to the Central Nervous System for the Virus of Herpes Simplex in Experimentally Infected Rabbits, Am. J. Path. **1**:11, 1925; The Pathways of Infection of the Central Nervous System in Herpetic Encephalitis of Rabbits Contracted by Contact, with a Comparative Comment on Medullary Lesions in a Case of Human Poliomyelitis, ibid. **1**:29, 1925. Goodpasture, E. W., and Teague, O.: Transmission of the Virus of Herpes Febrilis Along Nerves in Experimentally Infected Rabbits, J. M. Research **44**:139, 1923.

41. (*a*) Gantt, W. H., and Ponomarew, A. W.: Ueber den Mechanismus der Verbreitung des Tollwutvirus (Virus fixe) in Organismus, Ztschr. f. d. ges. exper. Med. **66**:582, 1929. (*b*) Goodpasture, E. W.: A Study of Rabies, with Reference to a Neural Transmission of the Virus in Rabbits, and the Structure and Significance of Negri Bodies, Am. J. Path. **1**:547, 1925.

causing hog cholera [42] and fowl plague,[6] enter the brain substance through the walls of injured blood vessels. In this connection it must be remembered that the mere presence of a virus in the circulation does not necessarily indicate, in case the brain is involved, that the portal of entry of the active agent into the nervous system is through the blood stream. For instance, when some viruses, such as vaccine virus,[20b] enter the general circulation they become highly concentrated on the nasal mucous membranes and from this point may travel to the brain by way of the nerves themselves or by their perineural spaces.

Modes of Dissemination.—Once a virus has made its entrance into the central nervous system, knowledge of its spread from one part to another becomes of interest and importance. Several possible ways of dissemination come to mind immediately: (1) direct extension from one portion to an adjacent structure; (2) spread by means of the spinal fluid, and (3) growth of the viruses along axis-cylinders. Undoubtedly a small amount of extension of the active agents occurs through the contact of infected parts with uninfected areas. Yet this method can account for only a minor portion of the dissemination. Therefore, many workers, e. g., Seifried and Spatz,[43] because of the distribution of lesions in the nervous system, are inclined to believe that the viruses of poliomyelitis, epidemic encephalitis, rabies and Borna disease (group A, table) are spread through the brain and cord by means of the spinal fluid and its free communication with the perivascular spaces. Others, e. g., Greenfield,[17b] think that the causal agents of the demyelinizing maladies (group D) in which the distribution of the lesions is quite different from that observed in the diseases already mentioned are disseminated through the spinal fluid. Experiments recently conducted by Fairbrother and Hurst,[44] by Hurst [45] and by Jungeblut and Spring [46] seem to indicate clearly, however, that in poliomyelitis the major part of the spread of the virus through the central nervous system is not by way of the spinal fluid but along axis-cylinders.

42. Seifried, O.: Histological Studies on Hog Cholera: I. Lesions in the Central Nervous System, J. Exper. Med. **53**:277, 1931.

43. Seifried, O., and Spatz, H.: Die Ausbreitung der encephalitischen Reaktion bei der Bornaschen Krankheit der Pferde und deren Beziehungen zu der Encephalitis epidemica, der Heine-Medinschen Krankheit und der Lyssa des Menschen, Ztschr. f. d. ges. Neurol. u. Psychiat. **124**:317, 1930.

44. Fairbrother, R. W., and Hurst, E. W.: The Pathogenesis of, and Propagation of the Virus in, Experimental Poliomyelitis, J. Path. & Bact. **33**:17, 1930.

45. Hurst, E. W.: A Further Contribution to the Pathogenesis of Experimental Poliomyelitis: Inoculation into the Sciatic Nerve, J. Path. & Bact. **33**:1133, 1930.

46. Jungeblut, C. W., and Spring, W. J.: A Note on the Propagation of the Virus in Experimental Poliomyelitis, Proc. Soc. Exper. Biol. & Med. **27**:1076, 1930.

Paths of Exit.—For epidemiologic reasons, information regarding the mode of exit of viruses from an infected central nervous system is essential. Again there are several obvious routes. For instance, a virus may leave by way of the blood stream, by means of perineural spaces and through nerves. Exit, however, need not occur along one route only, and it is not always a simple matter to determine which way is used in any given instance. It has been shown that poliomyelitic virus placed in the brain of a monkey appears later in the nasal mucous membranes.[47] The presumption is that the active agent travels down through the olfactory perineural spaces or along the olfactory nerves themselves. There is another possible way, however. Small amounts of the virus from the brain having entered the general circulation might reach the nasal mucous membranes and become concentrated at that point.[47a] Although such a route is feasible, it seems an improbable one in certain of the virus diseases, as it has been demonstrated that rabic virus travels from an infected brain to the salivary glands and saliva not by way of the blood stream, but by means of the nerves.[16a] Some viruses, for example, the active agents causing vaccinia and herpes febrilis, unquestionably enter the general circulation in considerable amounts following intracerebral inoculation. Nevertheless, it has been shown by Nicolau and Galloway [48] and others that the incitants of rabies, vaccinia, herpes, poliomyelitis and Borna disease spread from an infected central nervous system centrifugally along peripheral nerves. Furthermore, not only the active agents but definite pathologic changes [48] have been demonstrated in these nerves.

To make a more comprehensive review at this time of work dealing with the routes by which the viruses attain entry into, dissemination through and exit from the central nervous system is impossible. Furthermore, generalizations should be omitted, because much of the experimental work so far has been conducted with only a few viruses. From what has been said, however, it is evident that further studies in this field are needed.

PATHOLOGY

In this discussion a detailed description of the pathologic changes produced by the activity of different viruses in the central nervous system is not desired. Nevertheless, several points are of sufficient general interest and importance to warrant consideration.

47. (*a*) Flexner, S.: The Mode of Infection in Epidemic Poliomyelitis, J. A. M. A. **59**:1371 (Oct. 12) 1912. (*b*) Flexner, S., and Lewis, P. A.: Epidemic Poliomyelitis in Monkeys: A Mode of Spontaneous Infection, ibid. **54**:535 (Feb. 12) 1910.

48. Nicolau, S.; Dimancesco-Nicolau, O., and Galloway, I. A.: Étude sur les septinévrites à ultravirus neurotropes, Ann. Inst. Pasteur **43**:1, 1929.

Spielmeyer [49] stated that the brain and cord are so constructed that they are capable of reacting to injury in only a limited number of ways. Thus, regardless of the nature of the exciting agents, the pathologic pictures produced by them tend to be more or less stereotyped. Furthermore, according to him, it is difficult at times to distinguish inflammatory reactions, particularly chronic ones, from degenerative processes. It is true that the distribution and the character of lesions found in some diseases, such as those in group A (table), are sufficiently alike to cause difficulty in arriving at a correct diagnosis either by means of sections from a limited number of areas of the central nervous system or through examination of pathologic material without consideration of clinical observations and inoculation experiments. In spite of these difficulties, however, it is in most instances an easy matter, by means of pathologic examinations alone, to distinguish the diseases in the table from pyogenic infections of the brain and cord, or to separate the maladies of group A, exemplified by poliomyelitis, from those of group D, exemplified by postvaccinal encephalitis. Moreover, to the trained neuropathologist differences between more closely related diseases, such as those in group A, are frequently discernible. For instance, intracellular pathologic changes of the nature of Negri bodies and intranuclear inclusions, by means of which accurate diagnoses of rabies and Borna disease respectively are made, must possess some specificity. Hence it seems obvious that, either because the brain is capable of exhibiting a certain amount of variety in its responses to the individuality of injurious agents or because of differences in the portals of entry and modes of dissemination used by these agents, much still can be accomplished by means of neuropathologic methods toward a better understanding of diseases of the central nervous system.

In the literature dealing with the pathologic changes in virus diseases of the brain and cord, particularly in poliomyelitis [50] and rabies, considerable space has been given to discussions of the location and the nature of the earliest lesions. Investigators in favor of the idea that viruses, having in some way reached the spinal fluid, are then distributed by this medium to different parts of the central nervous system believe that the meninges [51] sustain the primary injury, while the deeper structures are involved later. Furthermore, according to them, the damage to nerve cells is neither direct nor specific, but secondary,

49. Spielmeyer, W.: Infektion und Nervensystem, Ztschr. f. d. ges. Neurol. u. Psychiat. **123**:161, 1929-1930.

50. Wickman, I.: Acute Poliomyelitis (Heine-Medin's Disease), Nervous and Mental Disease Monograph Series, no. 16, translated by J. W. J. A. M. Maloney, New York, Nervous and Mental Disease Publishing Company, 1913.

51. Flexner, S., and Amoss, H. L.: Localization of the Virus and Pathogenesis of Epidemic Poliomyelitis, J. Exper. Med. **20**:249, 1914.

resulting from pressure exerted by the surrounding edematous tissues. Other workers, however, who are of the opinion that the viruses of poliomyelitis [45] and rabies [41b] enter the central nervous system through growth along axis-cylinders of nerves, are disposed to believe that the primary lesions are in the nerve cells and that the disintegration of these elements leads to inflammation, edema and perivascular infiltration in the surrounding tissues. The latter concept is gaining favor, and as concerns certain maladies promises to be the one generally accepted.

This discussion of the pathology of virus diseases should not be closed without a word concerning the term "neurotropic ectodermoses." [52] There is an undoubted affinity between cells and viruses. If these peculiar agents are obligate parasites and if they multiply in cells—there is evidence that many of them do—it is to be expected that some cells will attract them more than others will. Because of these obvious facts, certain workers have elaborated ingenious concepts of virus maladies in which cytotropic tendencies of the infectious agents have been overemphasized. For instance, the incitants of vaccinia and herpes have been labeled ectodermotropic and neurotropic.[52] It is true that these agents invade ectodermal cells and at times exhibit neurotropic tendencies. Yet it must not be forgotten that they also attack, even in the brain, cells of other than ectodermal origin.[53]

IMMUNITY

A consideration of immunity is never a simple task, and in this respect a discussion of the phenomena associated with natural and acquired resistance of the central nervous system to viruses is not unique. In so far as is known, the nervous system becomes immune to the active agents at about the same time after exposure to them as do other parts of the body. Furthermore, the factors leading to a refractory state in the brain are probably similar to those operating in other organs. Much of this is conjecture, because the rôle in immunity played by the central nervous system has been sadly neglected. As a result of an incomplete understanding of the phenomena of immunity observed both in the brain and in other parts of the body, terms such as "lethal and non lethal autosterilization" [54] have been coined to act as a cloak for ignorance and for inability to establish a few favorite ideas regarding the etiology of certain diseases. This is no place, however,

52. Levaditi, C.: Ectodermoses neurotropes: Poliomyélite, encéphalite, herpès, Paris, Masson et Cie, 1922.

53. Goodpasture, E. W.; Woodruff, A. M., and Buddingh, G. J.: The Cultivation of Vaccine and Other Viruses in the Chorio-Allantoic Membrane of Chick Embryos, Science **74**:371, 1931.

54. Levaditi, C.; Sanchis-Bayarri, V., and Schoen, R.: Neuro-infections autostérilisables (encéphalite, herpès, rage), Compt. rend. Soc. de biol. **98**:911, 1928.

for a full discussion of the different facts, ideas and problems in the field of immunity. Therefore I shall pass immediately to a brief consideration of a more practical matter, the serum therapy of virus diseases.

Specific Serum Therapy.—Problems related to passive immunity and serum therapy have, needless to say, practical importance as well as theoretical interest. The clinician would like to know whether antiviral serums will protect contacts from virus diseases and cure the victims, while laboratory workers seek to determine in what way such serums are effective under certain conditions and why they fail at other times.

In regard to prophylaxis, it seems clear that the serums of persons convalescing from measles, varicella and yellow fever prevent these diseases respectively, provided they are given to susceptible contacts soon after exposure. If they are administered somewhat later, a mild disease ensues. When, however, the incubation period has passed, and signs and symptoms of infection have already made their appearance, considerable doubt exists as to how much the course of the maladies can be specifically altered even by enormous amounts of antiviral serum. This is also true of the hyperimmune serums prepared against vaccinia. In this connection one naturally thinks of the good results reported to follow the administration of convalescent serum in the treatment of poliomyelitis.[55] These reports must be given serious consideration. Most of the evidence, however, obtained in the laboratory by means of animal experimentation[56] and tissue cultures[57] points to the fact that, once a virus has attached itself to or has passed within a cell, the antibodies in a therapeutic serum encounter great difficulty in reaching it in effective doses. Therefore, workers in the laboratory reserve

55. Amoss, H. L., and Chesney, A. M.: A Report on the Serum Treatment of Twenty-Six Cases of Epidemic Poliomyelitis, J. Exper. Med. **25**:581, 1917. Aycock, W. L., and Luther, E. H.: Preparalytic Poliomyelitis: Observations in One Hundred and Six Cases in which Convalescent Serum Was Used, J. A. M. A. **91**:387 (Aug. 11) 1928. Hurst, E. W.: The Occurrence of Intranuclear Inclusions in the Nerve Cells in Poliomyelitis, J. Path. & Bact. **34**:331, 1931. Silverman, A. C.: Acute Poliomyelitis in Syracuse, New York: Clinical Analysis of Five Successive Outbreaks from 1922 to 1929, with Special Reference to Epidemiology and Treatment with Serum, Am. J. Dis. Child. **41**:829 (April) 1931.

56. Andrewes, C. H.: Antivaccinial Serum: 1. Protection Against Generalisation in the Rabbit; 2. The Time Factor in Protection Experiments, J. Path. & Bact. **32**:265, 1929.

57. Andrewes, C. H.: Virus III in Tissue Cultures: II. Further Observations on the Formation of Inclusion Bodies; III. Experiments Bearing on Immunity, Brit. J. Exper. Path. **10**:273, 1929. Rivers, T. M.; Haagen, E., and Muckenfuss, R. S.: A Study of Vaccinal Immunity in Tissue Cultures, J. Exper. Med. **50**:673, 1929.

the right to raise the question as to whether the beneficial therapeutic results reported as occurring under such conditions are due to specific antigen antibody reactions.

SUMMARY

In this paper I have not attempted to settle any of the lively disputes now in progress regarding the relation of filtrable viruses to diseases of the central nervous system. Nor have I proposed any theories of my own. My aim has been to present a tentative, yet working classification of the nervous disorders under discussion, to state briefly what is actually known about a few of them and, finally, to indicate some of the important problems concerning the etiology, pathogenesis, pathology, immunologic phenomena and treatment of these maladies in order that others may see them clearly in their proper perspective and take an active part in their solution.[58]

58. A complete bibliography appears in the author's reprints.

PATHOGENESIS OF THE CHANGES IN THE CEREBROSPINAL FLUID IN MENINGITIS

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The term "meningitis" as used in this paper is restricted to conditions in which living organisms are present in the cerebrospinal fluid. It includes the common forms of acute purulent meningitis, such as are caused by the meningococcus, the streptococcus, the pneumococcus and the staphylococcus, as well as tuberculous meningitis, acute syphilitic meningitis, influenza bacillus meningitis, colon bacillus meningitis and meningitis caused by mycoses.

In all these types of meningitis certain characteristic changes take place in the cerebrospinal fluid, namely, an increase in pressure, cells and protein, and a decrease in sugar and chlorides. It is the purpose in this paper to explain so far as is possible the mechanisms by which these alterations take place. Such an explanation, however, depends on a clear understanding of the nature of the cerebrospinal fluid.[1] In the light of present knowledge this may be summarized as follows: The cerebrospinal fluid is a protein-free [2] and lipoid-free dialysate in osmotic and hydrostatic equilibrium with the blood plasma. It is filtered into the ventricles from arterial blood in the capillaries of the choroid plexuses much as the glomerular filtrate is filtered from the glomerular capillaries into Bowman's capsule. The cerebrospinal fluid is thus analogous to the protein-free or protein-poor fluids that filter from the capillary beds throughout the organism to bathe and nourish the tissue cells. To this choroid plexus fluid there are probably added small amounts from the areae postremae described by Wislocki and Putnam,[3] from the intercolumnar tubercle described by Putnam,[4] from the perivascular spaces

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1. Fremont-Smith, F.: The Nature of the Cerebrospinal Fluid, Arch. Neurol. & Psychiat. **17**:317 (March) 1927.

2. Normal human ventricular fluid may contain as little as 5 mg. of protein per hundred cubic centimeters, an amount that is negligible when compared to the 7,000 mg. per hundred cubic centimeters in the plasma.

3. Wislocki, G. W., and Putnam, T. J.: Anat. Rec. **19**:281, 1920; **27**:151, 1924.

4. Putnam, T. J.: Bull. Johns Hopkins Hosp. **33**:181, 1922.

and possibly from other sources. There seems to be do doubt, however, that by far the largest part of the fluid is derived from the enormous capillary bed of the choroid plexuses.[5]

The normal rate of formation is unknown. The fluid circulates from the ventricles into the subarachnoid space, where it filters back into the blood, in part directly through the thin-walled veins and venules lying in the subarachnoid space but chiefly through the arachnoid villi that project from the subarachnoid space into the dural sinuses. Absorption along the cranial and spinal nerves may also occur. It is possible that some absorption takes place directly into the veins of the choroid plexus.

The normal cerebrospinal fluid pressure is the resultant of a delicate balance between the hydrostatic and osmotic pressures of the arterial blood in the capillaries of the choroid plexus and the venous blood in the dural sinuses.

The cerebrospinal fluid is analogous to the intercellular fluids of the organism, i. e., the true "milieu intérieure" of Claude Bernard. Meningitis is an infection of the cerebrospinal fluid. The results of such infection are parallel to the results of infection of the intercellular fluids elsewhere in the body. Acute meningitis may be called an empyema of the ventriculosubarachnoid system. The cerebrospinal fluid in meningitis is not to be distinguished from the fluid of an acute abscess; i. e., it consists of pus, except that in an abscess there is, in addition to the infection of the intercellular fluids, an actual breakdown of tissue cells, which rarely happens in meningitis. The increase in pressure and cells and the chemical changes in the cerebrospinal fluid in meningitis are all paralleled in an abscess. In fact, meningitis provides an unusual opportunity to study the effect of infection on the intercellular fluids, for here the normal fluid can be compared with the pathologic fluid. This is not possible in the case of an abscess elsewhere in the body, for the normal intercellular fluids are present in too small amounts to be studied.

CHANGES IN THE CEREBROSPINAL FLUID

1. *Increase in Pressure.*—Increase in pressure may be brought about by any factor that tends to increase the rate of formation or to decrease the rate of absorption, or otherwise to increase the volume of the cranial contents. In meningitis the rate of formation of cerebrospinal fluid is increased by: (1) dilatation of the vessels of the choroid plexus, leading to increased filtration pressure (?); (2) decrease in the osmotic pressure of the blood, and (3) increase in the osmotic pressure of the cerebrospinal fluid (?).

5. It should be noted that the choroid plexuses of the fourth ventricle extend through the foramina of Luschka into the cerebellopontile cisterns, and are therefore a source of both ventricular and extraventricular fluid.

The rate of reabsorption is decreased by: (1) obstruction by exudate of the cerebrospinal fluid pathways or of the arachnoid villi; (2) inflammatory reaction in the arachnoid villi; (3) decrease in the osmotic pressure of the blood, and (4) increase in the osmotic pressure of the cerebrospinal fluid (?).

The volume of the intracranial contents is increased by: (1) dilatation of the meningeal blood vessels and (2) edema of the brain (?).

There is no direct evidence that in meningitis the vessels of the choroid plexus are dilated during life. The appearance of these vessels, however, at autopsy, as well as the appearance of the meningeal vessels, makes such dilatation probable. If the arterioles of the choroid plexus are dilated, the capillary pressure and the filtration pressure of the choroid plexus will be increased.

At the onset of many acute infections the blood becomes hypotonic. Fremont-Smith, Dailey and Thomas have demonstrated that this occurs also at the onset of typhoid vaccine fever and malaria, owing to a retention in the body of ingested water.[6] A similar dilution of the blood follows the injection of the antidiuretic principle of the posterior lobe of the pituitary gland.[7] Weed [8] showed in animals that when the blood is rendered hypotonic by intravenous injection of distilled water, there is a rise in cerebrospinal fluid pressure. This has been demonstrated in man by Solomon, Thompson and Pfeiffer.[9] I believe that such an increase in cerebrospinal fluid pressure occurs at the onset of many acute infections as a result of the dilution of the blood and that this mechanism probably accounts for the increased cerebrospinal fluid pressure in meningism. This has been also suggested by Howe.[10] As most cases of acute meningitis begin with an acute febrile reaction, a similar mechanism may help to explain the high cerebrospinal fluid pressure found in the earliest stages of acute meningitis.

The splitting of dextrose (and possibly of protein) into several smaller molecules in the cerebrospinal fluid in meningitis as the result of glycolytic (and proteolytic) enzymes should tend to increase the total molecular concentration of the cerebrospinal fluid and hence raise its osmotic pressure. This factor may be another cause of increased

6. Fremont-Smith, F.; Dailey, M. E., and Thomas, G. W.: J. Clin. Investigation **6**:9, 1928.

7. Fremont-Smith, F.; Putnam, T. J., and Cobb, S.: Forced Drainage of the Central Nervous System: Its Effect on Blood and on Cerebrospinal Fluid, Arch. Neurol. & Psychiat. **23**:219 (Feb.) 1930.

8. Weed, L. H.: Physiol. Rev. **2**:171, 1922.

9. Solomon, H. C.; Thompson, L. J., and Pfeiffer, H. M.: J. Nerv. & Ment. Dis. **59**:474, 1924.

10. Howe, H. S.: Physiologic Mechanism for Maintenance of Intracranial Pressure, Arch. Neurol. & Psychiat. **20**:1048 (Nov.) 1928.

cerebrospinal fluid pressure. Thus the falling osmotic pressure of the blood would tend to raise the cerebrospinal fluid pressure by increasing the rate of fluid formation and decreasing its rate of absorption until the cerebrospinal fluid again reached equilibrium with the blood. This effect would be further accentuated by any factor tending to increase the osmotic pressure of the cerebrospinal fluid.

The mechanical effect of the exudate in interfering with the circulation and absorption of the cerebrospinal fluid needs no special comment. The inflammatory reaction within the arachnoid villi in acute meningitis has been demonstrated by Winkelman and Fay.[11]

The evidence that the cerebral vessels, and particularly the meningeal vessels, are dilated in acute meningitis is chiefly obtained at autopsy. Such dilatation is to be expected in the presence of inflammation. The resulting increase in cerebral blood volume must increase intracranial pressure. If this dilatation involves the arterioles of the brain, the capillary pressure will be increased, fluid will filter into the brain substance, and edema of the brain will result. It is probable that this plays a rôle in the production of increased cerebrospinal fluid pressure in meningitis.

It will be seen that all these causes of increased cerebrospinal fluid pressure in meningitis will be active in increasing the pressure within an abscess cavity. When the abscess is in a tissue not surrounded by a relatively inelastic covering like the dura, the rise in pressure will be less marked than in the case of the cerebrospinal fluid.

With present knowledge it is not possible to evaluate the relative importance of these various factors. It is evident, however, that there are a number of mechanisms tending to raise the cerebrospinal fluid pressure in meningitis.

2. *Increase in Cells.*—A detailed discussion of the increase of cells in the cerebrospinal fluid in meningitis is beyond the scope of this paper. A new advance in this field has been made by Kubie [12] by application of the vital staining methods of Sabin to the cerebrospinal fluid. It will suffice to say that in meningitis there is a pouring into the cerebrospinal fluid of the elements of the blood usually found in acute inflammation, together with some cells derived from the arachnoid.

3. *Increase in Protein.*—One of the earliest responses to inflammation is an increased permeability of the regional blood vessels so that they become permeable to protein.[13] Such an increased permeability of the blood vessels of the meninges and probably of the choroid plexus occurs in the earliest stages of meningitis, resulting in an increase in

11. Winkelman, N. W., and Fay, T.: The Pacchionian System, Arch. Neurol. & Psychiat. **23**:44 (Jan.) 1930.

12. Kubie, L. S., and Shults, G. M.: Bull. Johns Hopkins Hosp. **37**:91, 1925.

13. Menkin, V.: J. Exper. Med. **52**:201, 1930.

the albumin and globulin content of the fluid and the appearance of fibrinogen which is normally excluded from the cerebrospinal fluid. In addition, the breakdown of the cellular exudate probably plays a minor rôle in the increase in protein.

4. *Decrease in Sugar.*—The low sugar content of the cerebrospinal fluid in meningitis has been known since the work of Denigés and Sabrazés.[14] Mestrezat [15] was the first to recognize the two causes for such lowering, namely, destruction of dextrose by the bacteria and by the cellular exudate. That the bacteria are much the more important cause of the glycolysis has been demonstrated by Kelley [16] and by Fremont-Smith and Dailey.[17] Moderate increases of white blood cells in the cerebrospinal fluid, even up to several thousand per cubic millimeter, may be accompanied by normal sugar values provided no bacteria are present. Occasionally, however, with such high cell counts I have seen low cerebrospinal fluid sugar values in cases of brain abscess and sinus thrombosis, and in one case of tumor of the brain, in which no bacteria were recovered in smear or culture.

The low sugar content of the cerebrospinal fluid is in marked contrast to the sugar content of the blood, which is often elevated in meningitis. Hopkins [18] called attention to this fact in 1915. In the series already reported by Fremont-Smith, Dailey, Merritt and Carroll [19] the plasma sugar was above 150 mg. per hundred cubic centimeters in seven of twenty-six cases of tuberculous meningitis, in four of seven cases of pneumococcus meningitis and in four of seven cases of streptococcus meningitis; but in eight cases of meningococcus meningitis the highest sugar value was 132 mg. per hundred cubic centimeters. Thus, in fifteen of forty-eight cases the plasma sugar exceeded 150 mg. per hundred cubic centimeters. The highest value was 226 mg. per hundred cubic centimeters in a case of pneumococcus meningitis. The spinal fluid sugar at the same time was 94 mg. per hundred cubic centimeters, a value that would not have been considered low had the blood sugar value not been known. Thus, as suggested by Hopkins,[18] this hyperglycemia may raise the spinal fluid sugar in the earliest stages of meningitis and for a time completely mask the local breakdown of sugar in the spinal fluid.

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14. Denigés, G., and Sabrazés: Rev. de méd., Paris **16**:833, 1896.

15. Mestrezat, W.: Le liquide céphalo-rachidien, Paris, A. Maloine et fils, 1912.

16. Kelley, A. G.: South. M. J. **16**:407, 1923.

17. Fremont-Smith, F., and Dailey, M. E.: Cerebrospinal Fluid Sugar and the "Streptococcus of Poliomyelitis," Arch. Neurol. & Psychiat. **25**:206 (Jan.) 1931.

18. Hopkins, A. H.: Am. J. M. Sc. **149**:254; **150**:847, 1915.

19. Fremont-Smith, F.; Dailey, M. E.; Merritt, H. H., and Carroll, M. P.: The Equilibrium Between Cerebrospinal Fluid and Blood Plasma, Arch. Neurol. & Psychiat. **25**:1290 (June) 1931.

In the ventricular fluid the sugar may not be lowered as much as in the lumbar fluid, even when the ventricular fluid contains large numbers of organisms. This is probably due chiefly to the large surface afforded by the capiliary bed of the choroid plexus, allowing sugar from the blood to diffuse rapidly into the ventricular fluid. This phenomenon is well illustrated by the following tragic accident which occurred in 1925. A patient with a cerebellar glioma showed, at combined lumbar and ventricular puncture, a fasting plasma sugar of 82 mg. per hundred cubic centimeters, a ventricular fluid sugar of 64 mg. and a lumbar fluid sugar of 58 mg. Streptococcus meningitis developed following an operation, both lumbar and ventricular fluids containing many organisms. Three days after the first punctures, the plasma sugar was 195 mg., the ventricular fluid sugar was 130 mg., and the lumbar sugar was 13 mg. per hundred cubic centimeters.

It should be emphasized that a knowledge of blood sugar values is essential to the correct interpretation of the spinal fluid sugar values, especially in borderline cases.

5. *Decrease in Chlorides.*—The chloride content of normal cerebrospinal fluid is considerably higher than that of the blood plasma, normal values ranging in the cerebrospinal fluid from 436 to 455 mg. and in the plasma from 345 to 376 mg. per hundred cubic centimeters. (These chloride values, when expressed as sodium chloride, are equivalent to from 720 to 750, and from 570 to 620 mg., respectively, per hundred cubic centimeters. Since the potassium, calcium and magnesium ions present in body fluids may also combine with the chloride ions, the usual custom of expressing chloride values as sodium chloride is incorrect.)

Nobécourt and Voisin [20] were the first to note the lowering of the cerebrospinal fluid chlorides in meningitis, and furthermore Voisin [21] found that the more marked the lowering of the cerebrospinal fluid chlorides during life, the greater will be the meningeal reaction at autopsy.

Mestrezat [15] called attention to the diagnostic significance of the decrease in chlorides. He is responsible also for the first understanding of the normal relationship between plasma and cerebrospinal fluid chlorides and of the mechanism by which the decrease in cerebrospinal fluid chlorides in meningitis takes place. He pointed out that the cerebrospinal fluid has the same freezing point as the plasma and is hence isotonic with the plasma, but contains almost no colloids. The higher chloride content in the cerebrospinal fluid, he stated, is necessary to compensate for the absence of colloids in order that the cerebrospinal fluid may

20. Nobécourt, P., and Voisin, R.: Arch. gén. de méd. **2**:3018, 1903.

21. Voisin, R.: Thèse de Paris, 1904, no. 203.

have the same osmotic pressure as the plasma. He therefore called the cerebrospinal fluid an equilibrated dialysate ("dialysat equilibré"). It is interesting that in the same year, 1911, when Mestrezat published this in his Thèse de Montpellier, Donnan published a mathematical treatment of the same phenomena,[22] i.e., of the distribution of ions across a membrane which is impermeable to one of the ions but is permeable to the others.

It is necessary to keep in mind the dependence of the greater quantity of chloride in the cerebrospinal fluid on the greater quantity of colloids (chiefly proteins) in the blood plasma if one is to understand the mechanisms underlying the lowering of the cerebrospinal fluid chlorides in meningitis. Mestrezat reasoned that, since the normally high cerebrospinal fluid chloride values as compared to the plasma resulted from the impermeability of the choroid plexus and meningeal vessel membranes to colloids (chiefly proteins), any condition (viz., meningitis) making these vessels permeable and allowing protein to increase in the cerebrospinal fluid would result in a lowering of the cerebrospinal fluid chlorides; i.e., the composition of the cerebrospinal fluid would approach that of the plasma. Cohen [23] also accepted this point of view, as have most subsequent writers.

In 1924, Miss M. E. Dailey and I began an investigation of this subject. It soon became evident that there was no quantitative relationship between the increase in protein and the decrease in chloride in the cerebrospinal fluid in meningitis. This is strikingly seen in cases of meningitis reports of which have already been published by my associates and me.[19] Of the eighty-nine spinal fluids studied, twenty had chloride values of 375 mg. (620 mg. as sodium chloride) per hundred cubic centimeters or less, values within the range of normal plasma chlorides. Were such a decrease in spinal fluid chlorides due to increased permeability of the choroid plexus and meninges, it should be accompanied by an enormous increase in spinal fluid protein. In fact, the spinal fluid protein should approximate the plasma protein, i. e., from 6,000 to 8,000 mg. per hundred cubic centimeters. Actually, the highest spinal fluid protein content in this group of twenty cases was 800 mg., while only one other had a protein content above 380 mg., the averge protein content of the spinal fluid being 267 mg., while the average protein value of the plasma (determined in eleven of the twenty cases) was 7,100 mg. It will be seen that in these cases with the spinal fluid chloride content lowered to the normal plasma chloride level, in spite of a moderate increase in spinal fluid protein the spinal fluid remains relatively protein-poor when compared to the plasma, containing on the

22. Donnan, F. G.: Ztschr. f. Elektrochem. **17**:572, 1911.

23. Cohen, H.: Quart. J. Med. **17**:289, 1924.

average less than 4 per cent of the protein content of the plasma. (Normally it contains less than 0.4 per cent of the protein content of the plasma.)

It is evident that the increase in protein in these cases is not sufficient to account for more than a fraction of the decrease in chlorides actually observed. This is further borne out by the fact that, when the protein of the spinal fluid is increased to a similar degree in diseases other than meningitis, the decrease in chlorides is slight. A group of thirteen such cases,[24] with protein contents ranging from 225 to 2,084 mg., with an average of 546 mg. per hundred cubic centimeters, had an average chloride value of 423 mg. (as sodium chloride, 698 mg.) per hundred cubic centimeters.

The explanation for the low chloride content of the spinal fluid in meningitis is found as soon as the plasma chlorides are studied. My associates and I found a marked lowering in the plasma chlorides in meningitis,[19] which is nearly always sufficient to account for most of the decrease in spinal fluid chlorides. This was mentioned in a preliminary report before this association in 1924.[25] Mestrezat[15] had mentioned that a decrease in plasma chlorides might play some rôle, especially in tuberculous meningitis. It is remarkable, however, that previous to the report of Fremont-Smith and Dailey the study of the plasma chlorides had been almost wholly neglected in the search for the cause of the low spinal fluid chloride values in meningitis. Since then, Linder and Carmichael[26] and Wright, Herr and Paul[27] have reported low values for plasma chlorides in a few cases of meningitis, confirming our findings. Our data,[28] comprising two hundred and forty comparative studies of plasma and cerebrospinal fluid chlorides in patients without meningitis and eighty-nine such studies in patients with meningitis, make it clear that the chief cause for variations in the chloride content of the spinal fluid is variations in the plasma chlorides, and that the plasma chlorides are nearly always low in acute purulent and tuberculous meningitis; moreover, whenever the plasma chlorides are decreased in the absence of meningitis (as in acute febrile diseases, excessive vomiting, etc.), the spinal fluid chlorides are also decreased, often to as low levels as are found in meningitis.

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24. Fremont-Smith, F.; Dailey, M. E.; Merritt, H. H.; Carroll, M.P., and Thomas, G. W.: Equilibrium Between Cerebrospinal Fluid and Blood Plasma, Arch. Neurol. & Psychiat. **25**:1271 (June) 1931.

25. Fremont-Smith, F., and Dailey, M. E.: Cerebrospinal Fluid Chlorides, Arch. Neurol. & Psychiat. **14**:509 (Oct.) 1925; Proc. A. Research Nerv. & Ment. Dis., 1926, vol. 4, p. 111.

26. Linder, G. C., and Carmichael, E. A.: Biochem. J. **22**:46, 1928.

27. Wright, S. L.; Herr, E. F., and Paul, J. R.: J. Clin. Investigation **9**:443, 1930.

28. Fremont-Smith et al. (footnotes 19 and 24).

Occasionally, however, especially in the presence of subarachnoid block, the protein content in the spinal fluid may become greatly increased, i. e., over 500 mg. per hundred cubic centimeters. In such cases, whether meningitis is present or not, a slight reduction in spinal fluid chlorides is to be expected. Such a high protein content is rare in meningitis, and even when present plays a minor rôle in the decrease in chlorides.

Another factor, also mentioned in our earlier report,[25] probably plays a rôle in the decrease in chlorides. There is marked hydrogen ion concentration in the spinal fluid as the result of the breakdown of dextrose into lactic acid and carbonic acid.[29] On theoretical grounds one would expect this to upset the Donnan equilibrium between plasma and cerebrospinal fluid, leading to a decrease in cerebrospinal fluid chlorides and bringing them nearer to the plasma chloride level. There are no data available to show how important this factor is.

Cohen [23] found that normally the inorganic phosphorus content of the cerebrospinal fluid is much lower than that of the plasma, but that in meningitis an increase in the cerebrospinal fluid phosphorus occurs without any increase in the phosphorus content of the plasma. He attributed this increase (correctly, I believe) to an increase in the permeability of the membrane separating the plasma from the cerebrospinal fluid.

Chiefly as the result of these studies, Cohen enunciated what has been called the law of meningitis, which is here quoted:

> In meningitis the chemical changes which occur in the cerebrospinal fluid are of four types:
>
> 1. An increasing concentration in the cerebrospinal fluid of those substances which are normally present in greater quantity in the blood.
> 2. A decreasing concentration in the cerebrospinal fluid of those substances which are normally present in greater quantity in the cerebrospinal fluid.
> 3. The presence in the cerebrospinal fluid of substances which though normally present in the blood are normally absent from the cerebrospinal fluid.
> 4. The passage into the cerebrospinal fluid of foreign substances injected into the blood which normally do not pass the choroid plexus.

Under heading 1, Cohen placed protein, inorganic phosphorus and cholesterol. He noted dextrose as the one exception, it being utilized by organisms and cells, and hence decreasing in the cerebrospinal fluid.

Under heading 2, Cohen placed chlorides. In a later paper [30] he showed that magnesium is normally present in the cerebrospinal fluid in slightly greater quantity than in the plasma and that this excess is decreased in meningitis.

Under heading 3, he placed fibrinogen.

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29. Levinson, A.: Cerebrospinal Fluid, ed. 3, St. Louis, C. V. Mosby Company, 1931. Glaser, J.: J. Biol. Chem. **69**:539, 1926.

30. Cohen, H.: Quart. J. Med. **20**:173, 1927.

Under heading 4, he mentioned: iodides which, when injected intravenously, hardly appear at all in the cerebrospinal fluid in normal persons, while in meningitis the increase in the cerebrospinal fluid is marked; nitrates which, when fed by mouth, are only slightly increased in the cerebrospinal fluid, while in meningitis a marked increase occurs, and agglutinins, which appear in the cerebrospinal fluid in meningitis and in meningeal irritation but are almost entirely excluded normally. To this group might be added fluorescein and hemolysins.

Cohen further stated:

> The above four groups of changes lead us to adopt the view that the main factor influencing the chemical composition of the cerebrospinal fluid in meningitis is the degree of damage to the cells of the choroid plexus and cerebral blood vessels by the invading virus or toxin. This impairs the vitality of these cells and increases their permeability, and thus causes the cerebrospinal fluid to approximate the blood plasma in chemical composition.

This is a clear statement of the situation and is correct, except for the fact that Cohen neglected the effect of changes in the composition of the blood. These we have shown are of utmost importance in relation to chlorides.

Cohen's conclusions should therefore be modified to read as follows:

The main factors influencing the chemical composition of the cerebrospinal fluid in meningitis are three:

1. *Changes in the composition of the blood plasma* (decrease in the plasma chlorides and increase in the plasma sugar, leading to decrease in the cerebrospinal fluid chlorides and slight increase or delayed decrease in the cerebrospinal fluid sugar).

2. *Local breakdown of dextrose in the cerebrospinal fluid,* chiefly as a result of bacterial, and to a lesser degree of cellular, action (decrease in sugar, increase in hydrogen ion concentration and increase in lactic acid, resulting in slight decrease in cerebrospinal fluid chlorides).

3. *Increase in the permeability of the membranes separating the blood plasma from the cerebrospinal fluid,* allowing the cerebrospinal fluid to approximate to a slight degree the composition of blood plasma (increase in protein, in inorganic phosphorus, in uric acid, in immunologic substances, etc.; slight decrease in chlorides and in magnesium).

SUMMARY

Meningitis is an empyema of the ventriculosubarachnoid space. The cerebrospinal fluid in meningitis has the composition of pus. The chief changes in the cerebrospinal fluid in meningitis are an increase in pressure, cells and protein and a decrease in sugar and chlorides.

The increase in pressure is due to several causes. The most important are: (1) dilatation of the intracranial blood vessels and (2) mechanical obstruction by the exudate and inflammatory reaction of the cerebrospinal fluid pathways.

Decrease in the osmotic pressure of the blood, increase in the osmotic pressure of the cerebrospinal fluid and edema of the brain may also play a rôle. The cellular exudate comes chiefly from the blood stream, and to a lesser extent from the arachnoid cells. It is the usual cellular response to infection.

In meningitis, as in health, the chemical composition of the cerebrospinal fluid depends chiefly on the composition of the blood plasma, the cerebrospinal fluid tending to remain in osmotic equilibrium with the blood. The chief change in composition of the blood plasma in meningitis is a lowering of the chlorides, which is reflected by a parallel fall in cerebrospinal fluid chlorides. A similar fall in cerebrospinal fluid chlorides occurs whenever the plasma chlorides are decreased, notably in acute febrile diseases, such as pneumonia, scarlet fever, etc. The decrease in plasma chlorides is the chief cause for the low cerebrospinal fluid chlorides in nearly all instances.

A second factor influencing the composition of the cerebrospinal fluid in meningitis is the local breakdown of dextrose as a result of bacterial and cellular action. This results in a lowering of the dextrose content of the cerebrospinal fluid, which may fall nearly to zero, and in an increase in acidity of the cerebrospinal fluid, chiefly due to an increase in lactic acid. This in turn results in a disturbance of the Donnan membrane equilibrium and tends to lower the chloride content of the cerebrospinal fluid, bringing it nearer to that of the blood.

In addition, there is a partial breakdown of the impermeability to protein of the membranes separating the plasma from the cerebrospinal fluid. This allows protein to enter the cerebrospinal fluid, raising its protein content, which results in lowering of the cerebrospinal fluid chlorides. As the protein content of the cerebrospinal fluid in meningitis is usually only moderately increased, so that when compared to plasma the cerebrospinal fluid remains relatively protein-poor, the effect of this increased permeability on the chloride distribution is usually slight and often negligible. Occasionally, however, especially in the presence of subarachnoid block, the protein content becomes markedly increased. Under these circumstances there is also the opportunity for the greatest accumulation of lactic acid. The cerebrospinal fluid chloride level may then become appreciably closer to that of the plasma.

Rarely this combined effect may be quantitatively greater in lowering the cerebrospinal fluid chlorides than the effect of the fall in plasma chlorides.

HISTOLOGIC STUDIES IN MENINGITIS

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The term meningitis denotes an inflammation of the cerebrospinal meninges. The common form is leptomeningitis, an acute inflammation of the pia-arachnoid; a much rarer type is pachymeningitis, an inflammation of the dura mater, which is a chronic condition. The former is represented by the purulent, tuberculous or cerebrospinal form, while pachymeningitis is usually the result of a constitutional disorder, syphilis and occasionally tuberculosis.

It is customary to include with the group of meningitis changes in the cerebrospinal membranes that are secondary to an invasion by spirochetes, Trichina, Torula and Cysticercus, and by carcinoma, sarcoma and other malignant growths. Whatever the etiologic factors, the meninges exhibit a manifest reaction. It pertains to the mesodermal components of the pia-arachnoid and dura, differing mainly in intensity and extensity.

THE PIA-ARACHNOID

In the pia, mainly of the spinal cord, Key and Retzius [1] differentiated two main layers: an external, inconstant one, consisting of parallel longitudinal fibers arranged in thick bundles and covered by thin membranes (*"Häutchen"*), and a more essential, internal layer, generally known as intima piae. This layer is always present and is made up of three sheaths, the external consisting of an elastic longitudinal network, the middle layer made up of circular fibers and the inner represented by a thin membrane closely investing the spinal cord. In some places, especially over the medulla, the intima piae harbors pigment cells (chromatophores). It (fig. 1) extends into the brain and cord, accompanying the blood vessels and forming their adventitial tunics. Injections into the subarachnoid spaces, for instance, carry the fluids along those pial prolongations, thus proving the existence of a communication

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1. Key, A., and Retzius, A.: Studien in der Anatomie des Nervensystems, Stockholm, P. A. Norstedt & Söner, 1875, vol. 1, p. 146.

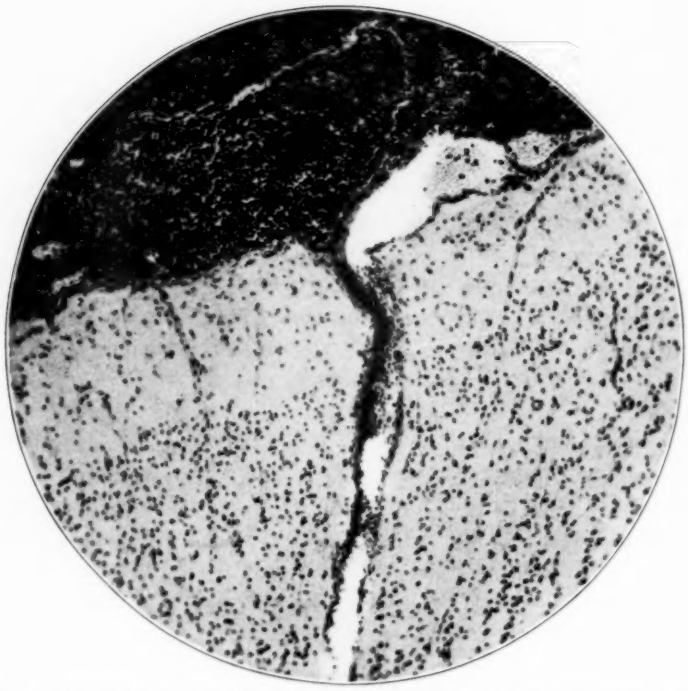

Fig. 1.—Purulent meningitis. The prolongations of the infiltrated pia invade the cerebral parenchyma. Toluidine blue stain.

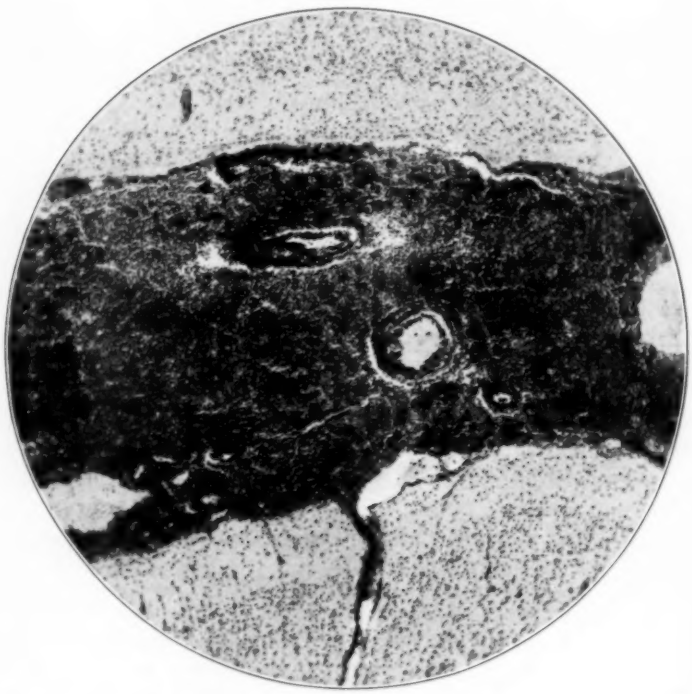

Fig. 2.—Purulent meningitis. The subarachnoid space is greatly distended. The vessels show a patent lumen and marked perivascular infiltrations. The infiltrations extend from the subarachnoid space along the pial prolongations as pictured in figure 1. Toluidine blue stain.

between the subarachnoid and Virchow-Robin spaces of the cerebral blood vessels. Key and Retzius, in emphasizing such a communication, clearly stated that through the latter a discharge of fluids is effected from the depths of the brain and cord into the subarachnoid spaces. Based mainly on experimental data, such a view is also supported by a number of facts from human pathology repeatedly discussed elsewhere.[2] They force one to the conclusion that the subarachnoid spaces are receptacles of the waste products discharged by the brain and cord.

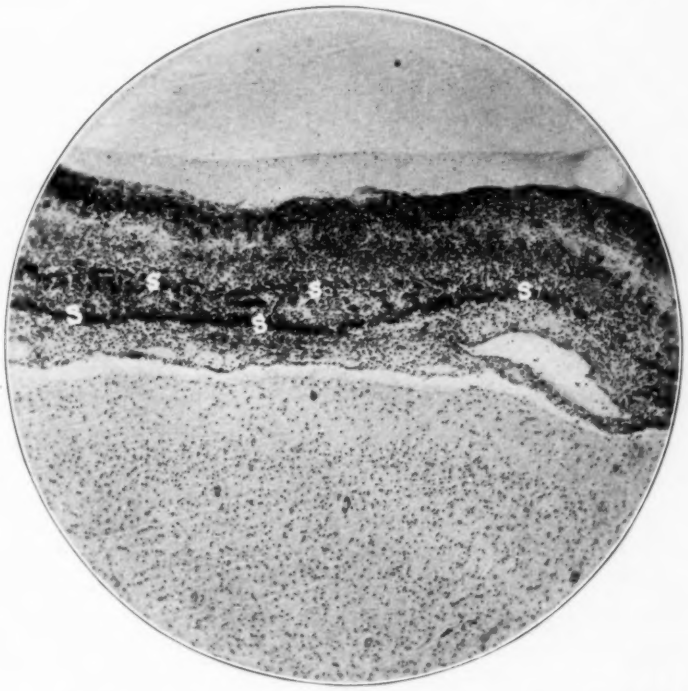

Fig. 3.—Purulent meningitis. Dense stripes (*S, S, S*) are visible in the lower half of the subarachnoid space and a pale band in the upper half of the picture. Toluidine blue stain.

However, the meningeal spaces are by no means open or free. Situated between the pia and arachnoid, they are traversed by dense masses of connective tissue strands or trabeculae. These form a spongy mass containing numerous blood vessels and innumerable channels which are lined with mesothelial cells and harbor the cerebrospinal fluid. The

2. Hassin, G. B.: (*a*) Notes on the Nature and Origin of the Cerebrospinal Fluid, J. Nerv. & Ment. Dis. **59**:113 (Feb.) 1924; (*b*) Effect of Organic Brain and Spinal Cord Changes on Subarachnoid Space, Choroid Plexus and Cerebrospinal Fluid, Arch. Neurol. & Psychiat. **14**:468 (Oct.) 1925.

mesothelial cells also cover the blood vessels and the avascular arachnoid membrane, thus forming a continuous lining. Unlike the pia, the arachnoid does not invade the brain or cord substance but, bridging the sulci, it accompanies the dura, protruding into it and forming villi or pacchionian bodies. In the presence of the foregoing anatomicohistologic features it is hard to conceive of the pia as anything but a mesodermal structure.

THE DURA

Like the pia-arachnoid, the dura is also a mesodermal, vascular, structure. Its noteworthy histologic features are lacunae and numerous narrow interstitial spaces containing nests of arachnoid (mesothelial) cells. Accompanied by the arachnoid membrane, subdural and subarachnoid spaces, the dura extends over the cranial nerves, the spinal roots and even the peripheral nerves. The latter thus possess the same membranes and spaces (called here perineurial) as the brain and spinal cord. Suitable fluids (liquid petrolatum or various oils containing suspensions of dyes or lampblack) injected into the peripheral nerves may reach the meninges and their spaces.[3] Such a continuous stretch of the cerebrospinal spaces from the center to the periphery is of great significance, especially in pathologic conditions. An inflammation of the peripheral nerves, for instance, may be conveyed to the central nervous system, and, vice versa, an inflammation of the meninges (meningitis) may reflect not only on the subjacent brain and cord but also on the spinal roots and the peripheral nerves, cerebral as well as spinal. In short, one may be confronted in meningitis with a number of problems. Some pertain to the reaction of various cell elements, normally present in the meninges; some to the extent of involvement of the perineurial spaces of the cranial nerves or spinal roots; some, again, pertain to the effect of the affected meninges on the brain or, vice versa, of the latter on the meninges and their spaces.

REACTIONS IN MENINGITIS

1. *Cell Reaction in Meningitis.*—Regardless of the type of meningitis, the characteristic feature is an increase in the number of cells. In some forms of meningitis the increase is immense; the subarachnoid meshes are so crowded (fig. 1) by the increased cell masses that the trabeculae and other markings become obliterated and the subarachnoid space becomes enormously expanded (fig. 2). In the dura the reaction is different. It is mainly in the form of proliferation of fibroblasts, an increase in their size, with the formation of foci of gitter cells in the

3. Funaoka, S.: Untersuchungen über das periphere Nervensystem, Serie A, Heft 1, Die Injektion des Nervensystems, Kyoto, Anatomical Institute of Kyoto Imperial University, 1930.

interspaces and cellular invasion of the epidural space. While an increased number of cells in a distended meningeal space generally suffices for the diagnosis of meningitis, the nature of the latter can be determined only from the type and character of the cells. This, however, is true only for some cases. As has been pointed out elsewhere,[4] the purulent and tuberculous forms may correctly be diagnosed in the

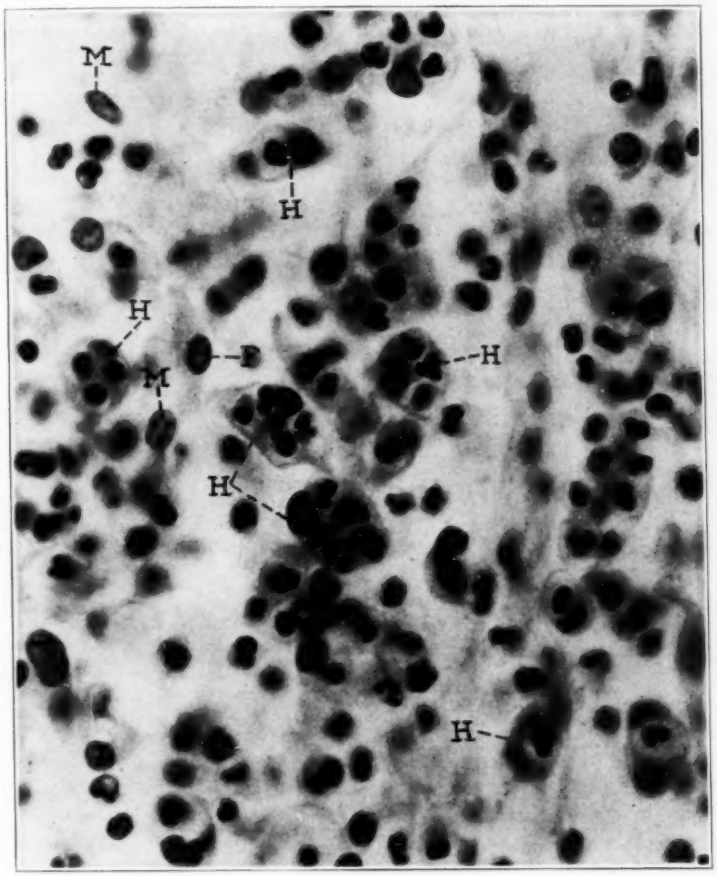

Fig. 4.—Purulent meningitis. *H, H,* histiocytes (macrophages); other cells explained in the text. *M, M,* mesothelial cells. *F,* a fibroblast. Hematoxylin-eosin stain.

majority of cases. But a differential diagnosis between the purulent and the meningococcus forms or between the tuberculous and syphilitic types is not always possible.

4. Hassin, G. B.: Cellular Changes in Various Forms of Acute Leptomeningitis, M. Rec. **93**:760 (May 4) 1918.

Purulent Meningitis: In this type the prevalent cells in the subarachnoid space are polymorphonuclears. They dominate the field, are often packed with micro-organisms and form dense foci. Occasionally, as figure 3 shows, they form distinct dense bands or stripes separated from one another by paler, necrotic areas containing masses of micro-organisms and broken-up, badly stainable, decomposed and ill defined cell bodies. The stripes themselves consist of masses of polymorphonuclear cells, a few lymphocytes, still fewer macrophages (histiocytes)

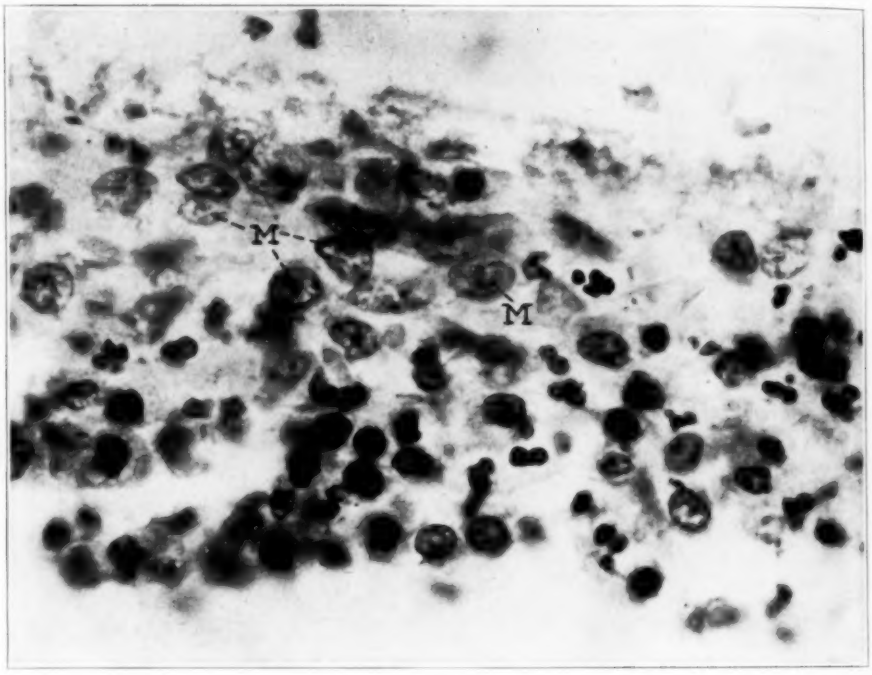

Fig. 5.—Purulent meningitis. The mesothelial cells *M*, *M*, of the arachnoid membrane are intermingled with polymorphonuclear elements and show no reaction. Hematoxylin-eosin stain.

and homogeneous globules and, scattered among them, foci of micro-organisms. The nuclei of the majority of the cells usually stain densely, but in some they are broken up and represented by only a few granules (karyolysis). No mesothelial cells are present in the stripes, but in the paler, necrotic areas they are occasionally found in a state of profound degeneration; they are exceedingly pale, practically colorless, and the nucleus is in a state of karyolysis. In areas in which pus cells are rare or absent, macrophages are numerous (fig. 4) and are intermingled with lymphocytes, plasma cells, gitter cells, mesothelial cells and fibroblasts.

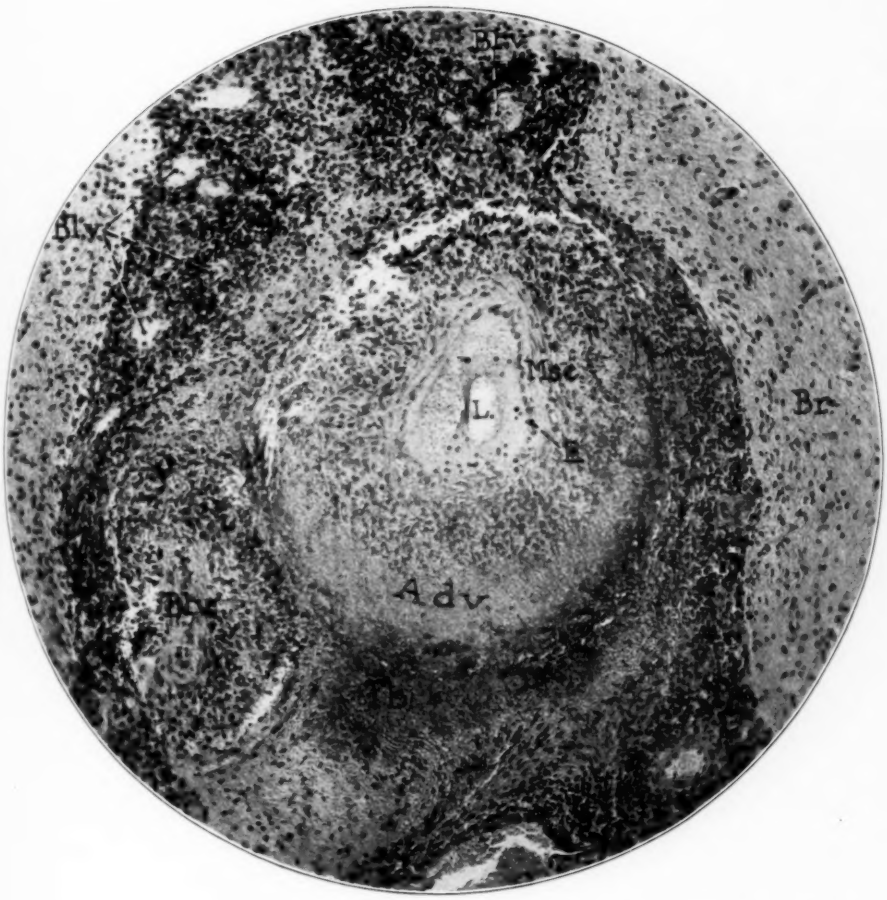

Fig. 6.—Tuberculous meningitis. The adventitia (*Adv.*) and part of the muscularis (*Msc.*) of the large blood vessel in the center are infiltrated, in the upper portion, with well stained cell elements; the left and especially the lower half of the adventitia, and to a lesser extent that of the muscularis, are either caseous at *Adv.* or in the process of becoming necrotic, merging with the adjacent tuberculous tissue (*Tb.*). The lumen (*L*) is patent and filled with blood and coagulated serum. The garland-like shape of the endothelium (*E*) is also well shown. At *Br.* is the brain tissue. Between this and the large central blood vessel at *Bl. v.* are several smaller blood vessels markedly infiltrated. Hematoxylin-eosin stain.

The inner layer of the pia, called by Cerletti [5] the zona vasalis—because of its wealth in blood vessels—is enormously hyperemic and infiltrated. As in inflammatory conditions of the brain, the infiltrations are confined to the adventitial spaces of Virchow-Robin and consist mainly of plasma cells and polyblasts. The former often show regressive changes and appear vacuolated. In other instances, they show progressive phenomena, when they exhibit more than one nucleus and may attain enormous dimensions (giant plasma cells). With lymphocytes they dominate the inner layer, while in the middle layer of the pia the fibroblasts prevail; the histiocytes, in the form of gitter cells, are much more common in the external layer of the pia. The histiocytes (macrophages) as well as the hypertrophied fibroblasts contain within their vacuoles pus cells, pigment granules and broken-up erythrocytes (fig. 4).

The arachnoid membrane shows, in areas of extensive purulent inflammation, numerous mesothelial cells but no cluster formations (fig. 5). The cells appear here oblong, narrow and somewhat uniformly stained. They show no changes in form that would indicate a formation of macrophages. In areas less affected by the suppurative process, the cisterna magna, for instance, the mesothelial cells are entirely normal. They form here clusters, but are frequently encountered also as single elements, especially in the deeper layers of the subarachnoid space (fig. 4). Here they appear irregular, biscuit-shaped or rod-shaped, mostly oval, and pale, and are mixed with dark stained lymphocytes, polymorphonuclears, fibroblasts and macrophages. It is rather remarkable how indifferently these cells behave toward the presence of pus cells or other pathologic products. Nowhere do they show any signs of transformation into macrophages or other progressive phenomena (fig. 5).

Tuberculous Meningitis: In this type the subarachnoid changes are altogether different. They are mainly vascular, with the formation of tubercles. The pial blood vessels are exceedingly numerous; their walls are hyperplastic and infiltrated with immense masses of cells (fig. 6) which, for the most part, stain badly or not at all. The type of the cells cannot always be determined. In some instances it is possible only with difficulty to discern lymphocytes, plasma cells and other elements. The vascular lumen is usually patent; the intima is represented by a chain of endothelial cells which is often detached from the media, separated from it by masses of lymphocytes, macrophages, gitter cells and polyblasts. Profound changes are present in the elastic membrane and media. The muscle fibers stain badly and are homogeneous and

5. Cerletti: Die histopathologische Veränderungen der Hirnrinde bei Malaria perniciosa, in Nissl and Alzheimer: Histologische und histopathologische Arbeiten ueber die Grosshirnrinde, Jena, Gustav Fischer, 1910, vol. 4.

hyaline-like, while the elastica is split and broken up into thin fibrils. The adventitia, in contrast, is hyperplastic and invaded by lymphocytes, plasma cells and fibroblasts, which may also extend to the media, transgress the elastic membrane and, as said, push the intima away from the media. The entire adventitial wall ultimately becomes densely infiltrated, and in far advanced cases the infiltrating masses become necrotic and caseous, probably because of insufficient blood supply caused by occlusion of the nutrient blood vessels.

The necrotic masses of the walls of the blood vessels usually merge with the surrounding tissues (fig. 6, at *Tb.*), which exhibit the same infiltrating elements and caseation as are present in the adventitial spaces. Polymorphonuclear cells are absent in uncomplicated cases of tuberculous meningitis, while plasma cells sometimes appear as pale nuclei, almost devoid of chromatin, which if present does not show a spokelike arrangement (fig. 7).

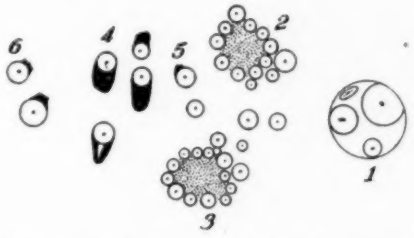

Fig. 7.—Tuberculous meningitis. Some of the types of cells occurring in tuberculous meningitis. *1*, a histiocyte (macrophage); *2,3*, degenerated plasma cells surrounding amyloid bodies; *4,5,6*, changed plasma cells. Toluidine blue stain.

The abnormal infiltrations of the adventitia of the blood vessels and the adjacent areas in tuberculous meningitis are analogous to what are generally described as tubercles. The center of a tubercle consists of broken-up, necrosed histiocytes or epithelioid cells; it is bordered by giant cells and a zone of inflammatory cells—lymphocytes and plasma cells. Like the central epithelioid cells, the peripheral layer undergoes regressive changes, ultimately appearing as a structureless, cheesy mass. The presence of tubercles and the vascular changes make the histologic picture of tuberculous meningitis quite typical. It sometimes resembles syphilitic gummatous meningitis from which it often cannot be differentiated.

Cerebrospinal and Pneumococcus Forms: In both these forms the distended meshes of the subarachnoid spaces also contain increased numbers of cells, among which polymorphonuclears are as frequent as the other types—lymphocytes, plasma cells, polyblasts, histiocytes and

fibroblasts. The blood vessels also show marked infiltrations which, like the intima piae, often consist only of plasma cells. In the middle and outer zones of the pia the prevailing elements are lymphocytes and polymorphonuclears, while areas poor in the latter are rich in macrophages, fibroblasts and rodlike cells.

Fig. 8.—Tuberculous meningitis. Invasion of the perineurial spaces (perineuritis) of the cerebral nerves. Toluidine blue stain.

The meningeal changes described are also present in the stroma of the choroid plexus. The cell masses may break through the tufts or assemble between them and the blood vessels. The tuft cells themselves appear homogeneous, in specimens stained with hematoxylin and eosin, but generally are altered only slightly.

A comparative study of the four most common types of meningitis shows a cell reaction that may be considered fairly uniform for any

form of meningitis, with the exception of the polymorphonuclears which are typical of the purulent and the cerebrospinal types; it is also fairly similar in other types of meningitis, subacute or chronic, including such forms as those caused by trichinosis, syphilis and cysticercal or torular invasion. The differences are mainly quantitative. The reactive

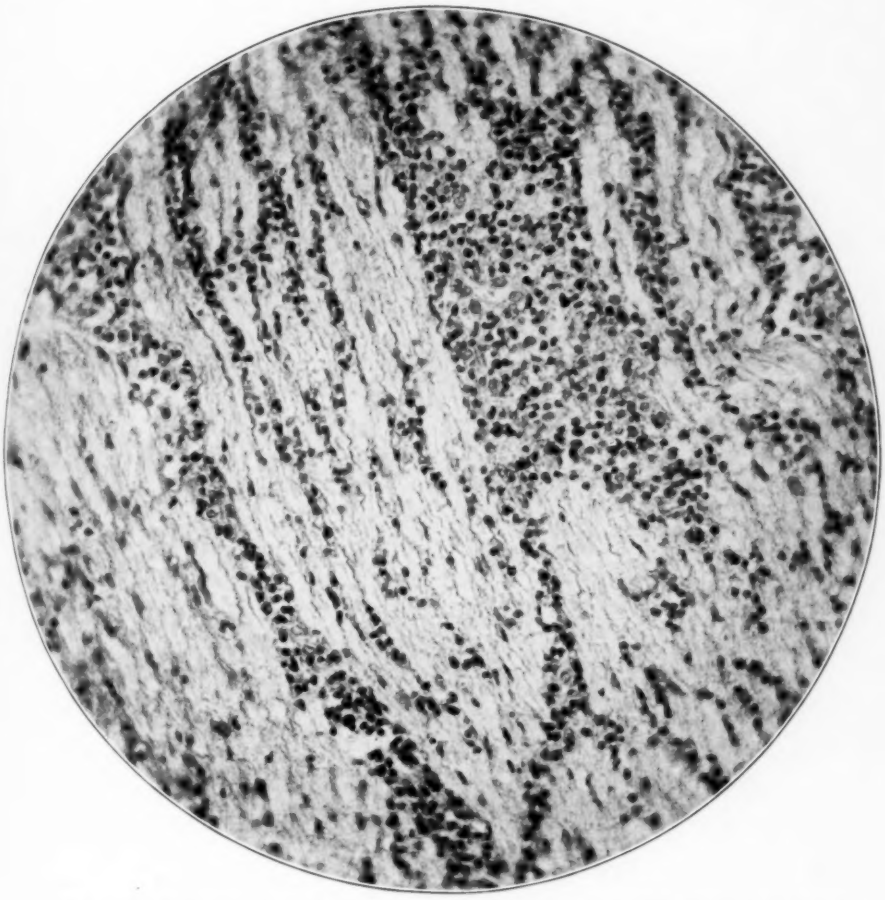

Fig. 9.—Purulent meningitis. Invasion of the endoneurial spaces by dense rows of cells, described in the text. Hematoxylin-eosin stain.

cells are either hematogenous—lymphocytes and their derivatives—or histiogenic (tissue cells)—fibroblasts and histiocytes (macrophages). The former are usually present in immense numbers and may overshadow not only the other group, the tissue cells proper, but also the normal subarachnoid structures: the trabeculae, arachnoid villi and mesothelial cells. These structures appear, as it were, drowned in the

enormous masses of pus cells that crowd the subarachnoid as well as the perineurial spaces (fig. 8) of the cranial nerves and the spinal roots. In short, a meningitis is more or less complicated by a perineuritis.

2. *Perineurial Changes.*—As the pictures (figs. 8 and 9) show, the inflammation invades the interior of the nerve, involving the endo-

Fig. 10.—Tuberculous meningitis. Dense infiltration of the subarachnoid space of the pons with infiltrated blood vessels of the superficial layers. Above to the left is a tubercle. Toluidine blue stain.

neurium (fig. 9); the types of the invading cells are the same as those present in the subarachnoid space. They surround the nerve fibers with the proliferated endoneural single cells and, in chronic or protracted cases, obstruct the perineurial passages, thus reflecting not only on the condition of the nerve fibers but also on that of the cerebrospinal

subarachnoid spaces and indirectly on the brain tissues. This has been discussed elsewhere.[6] An extension of the meningeal infiltrations to the perineurial root spaces occurs in any form of meningitis—classic purulent and tuberculous,[7] syphilitic, so-called carcinomatous,[8] sarcomatous and similar conditions.

Fig. 11.—Rarefaction of the brain tissue. Toluidine blue stain.

6. Hassin, G. B.: Hydrocephalus: Studies of the Pathology and Pathogenesis, with Remarks on the Cerebrospinal Fluid, Arch. Neurol. & Psychiat. **24**:1164 (Dec.) 1930.

7. Loewenstein, G.: Ueber die Veränderungen des Gehirns und Rückenmarks bei der Meningitis cerebrospinalis epidemica, Beitr. z. path. Anat. u. z. allg. Path. **47**:282, 1910.

8. Walshe, F. M. R.: A Case of Secondary Carcinomatous Infiltration of the Pia-Arachnoid of the Brain, Presenting Exclusively Ocular Symptoms During Life: Meningitis Carcinomatosa, Brit. J. Ophth. **7**:113 (March) 1923.

3. *The Effect of Meningitis on the Brain.*—As I have emphasized elsewhere,[6] an obstruction of the perineurial spaces interferes with the discharge of the spinal fluid, ultimately resulting in the formation of rarefaction, hydrocephalus and edema of the brain. Much, of course, depends on the extent of the involvement of the subarachnoid space. As the latter and the Virchow-Robin spaces of the cerebral blood

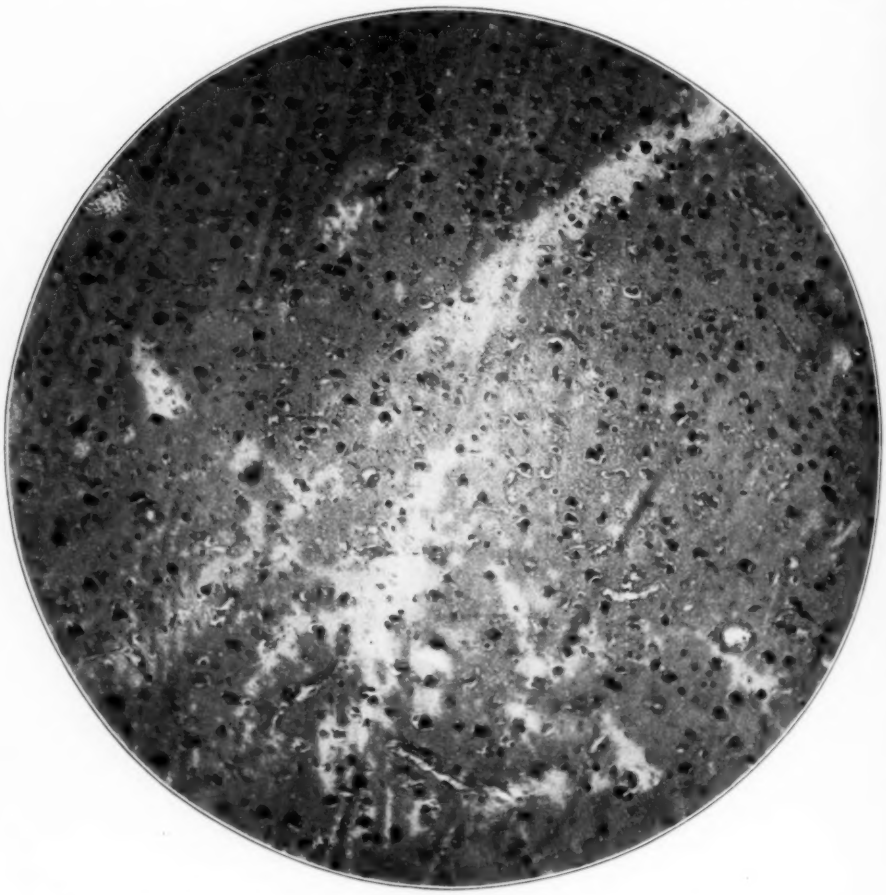

Fig. 12.—Tuberculous meningitis. The pale areas are described in the text. Toluidine blue stain.

vessels form one system, it is only natural to postulate an invasion of the cerebral or spinal parenchyma by the contents of the subarachnoid space—tubercles in tuberculous meningitis, and pus or carcinoma cells in purulent or carcinomatous involvement of the subarachnoid space. This actually takes place, but only in the superficial layers of the brain, provided the subarachnoid spaces are overcrowded by pathologic ele-

ments (fig. 10). In ordinary conditions, the latter are prevented from invading the cerebral Virchow-Robin spaces, probably by the contents of the latter which flow toward the subarachnoid spaces, discharging into or being drained by them. The inability to discharge the contents of the Virchow-Robin spaces results in an accumulation of fluids in the tissue spaces, their rarefaction and distention, and the formation of

Fig. 13.—Cerebral softening. Pale areas in the pons. Toluidine blue stain.

vacuoles (fig. 11). The changes are the more evident, the more crowded the subarachnoid spaces. If these are only slightly involved, the draining of the cerebral parenchyma goes on and the phenomena of stasis and rarefaction of brain tissues are either absent or very mild. When present, they are, in my opinion, the most important and dangerous cerebral complications of meningitis, for the stagnant fluids of the distended tissue spaces, surcharged with catabolic substances, cause

degenerative changes in the ganglion cells and nerve fibers. Nerve tissue, as demonstrated by Rumpf experimentally,[9] cannot exist in stagnant tissue fluids.

Of other cerebral changes occurring in meningitis, pale areas (fig. 12), lately emphasized by Wertham [10] in purulent meningitis, should be

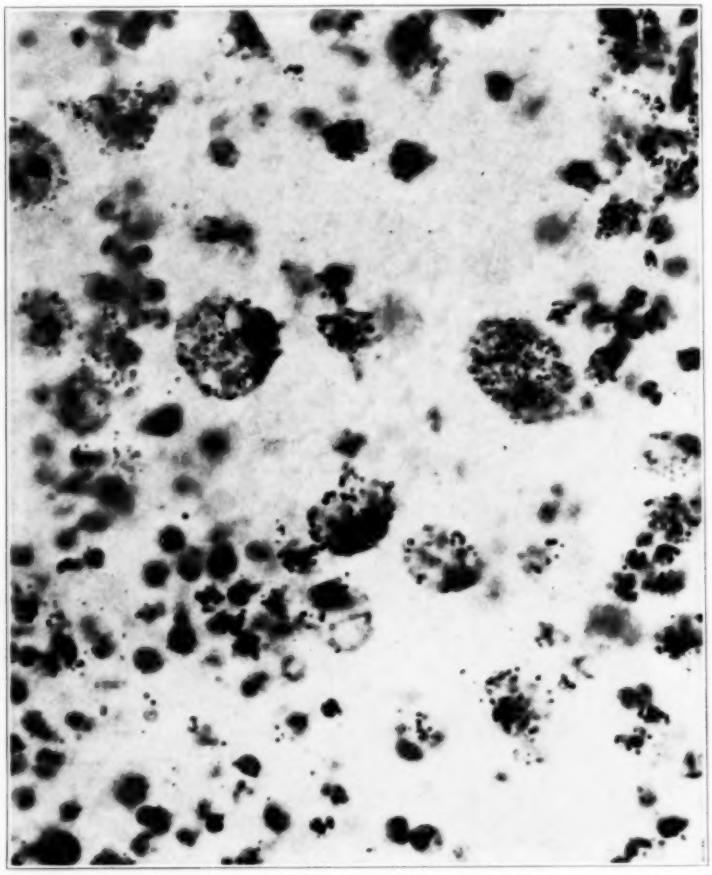

Fig. 14.—Subarachnoid space from a case of multiple cerebral hemorrhages. Histiocytes (macrophages) packed with blood pigment. Toluidine blue stain; × 650.

mentioned. They appear as streaks or spots from which some ganglion cells have dropped out; others are very pale and shrunken, stain poorly, show the severe cell disease of Nissl or ischemic cell changes and

9. Rumpf, T.: Ueber die Einwirkung der Lymphe auf die Centralorgane, Arch. f. d. ges. Physiol. **26**:415, 1881.

10. Wertham, F.: The Cerebral Lesions in Purulent Meningitis, Arch. Neurol. & Psychiat. **26**:549 (Sept.) 1931.

possess a pyknotic nucleus. The glia often shows as very small, dark nuclei usually exhibiting regressive changes. Wertham also spoke of areas of demyelinization and vascular changes (occasional perivascular infiltrations). As to the pale areas, I wish merely to point out that they may occur in other pathologic conditions—inflammatory, tuberculous or cerebrospinal meningitis (Sittig,[11] Bodechtel and Opalski [12]) or degenerative conditions (multiple sclerosis, for instance). They were in my specimens associated with areas of rarefaction and like these can, in my opinion, be considered the result of stagnation of tissue fluids. Figure 13, from a case of cerebral softening (pons), shows the pale areas even more clearly and outstandingly than in the worst cases of meningitis. Wertham considered that the pale areas are responsible for the residual phenomena—clinical and pathologic—observed in patients who have recovered from purulent meningitis. Yet, so far as I am aware, they have not been demonstrated in patients in whom "recovery occurs from purulent meningitis" and who exhibit various sequelae.

THE EFFECT OF THE PARENCHYMAL CHANGES ON THE MENINGES

It is evident that if the cerebral parenchyma discharges metabolic or other substances into the subarachnoid space, the latter should show some reactive phenomena. In many ways, these resemble a meningitis. In figure 14, for instance, are shown the subarachnoid space changes in a case of a meningeal hemorrhage. Masses of histiocytes, filled with blood pigment and scattered among numerous lymphocytes, plasma cells, fibroblasts and mesothelial cells, crowd the meshes of the subarachnoid space. The mesothelial cells appear mostly as very pale cells, single or gathered in small clusters; some show as smaller and darker nuclei, but, as in frank cases of meningitis, they show no morphologic changes suggestive of phagocytic activities. Figure 15 is from a case of softening of the brain. Here the subarachnoid space is extremely cellular and is dominated by gitter cells, which, as in the case of hemorrhage, are mixed with lymphocytes and other cells. I could present many more instances to demonstrate the effect of brain changes on the meninges, for there is hardly a pathologic condition in the brain that would not produce some meningeal reaction. Some such instances were cited in a contribution before the Association for Research in Nervous and Mental Diseases in 1924.[2b] These were instances of subarachnoid changes caused by changes in the brain that were typical morphologically and therefore easily demonstrable.

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11. Sittig, O.: Ueber herdförmige Destruktionsprozesse im Grosshirn und Veränderungen im Kleinhirn bei tuberkulöser Meningitis, Ztschr. f. d. ges. Neurol. u. Psychiat. **23**:511, 1914; **33**:294 and 301, 1916.

12. Bodechtel, G., and Opalski, A.: Gefässbedingte Herde bei der tuberkulösen Meningitis, Ztschr. f. d. ges. Neurol. u. Psychiat. **125**:401, 1930.

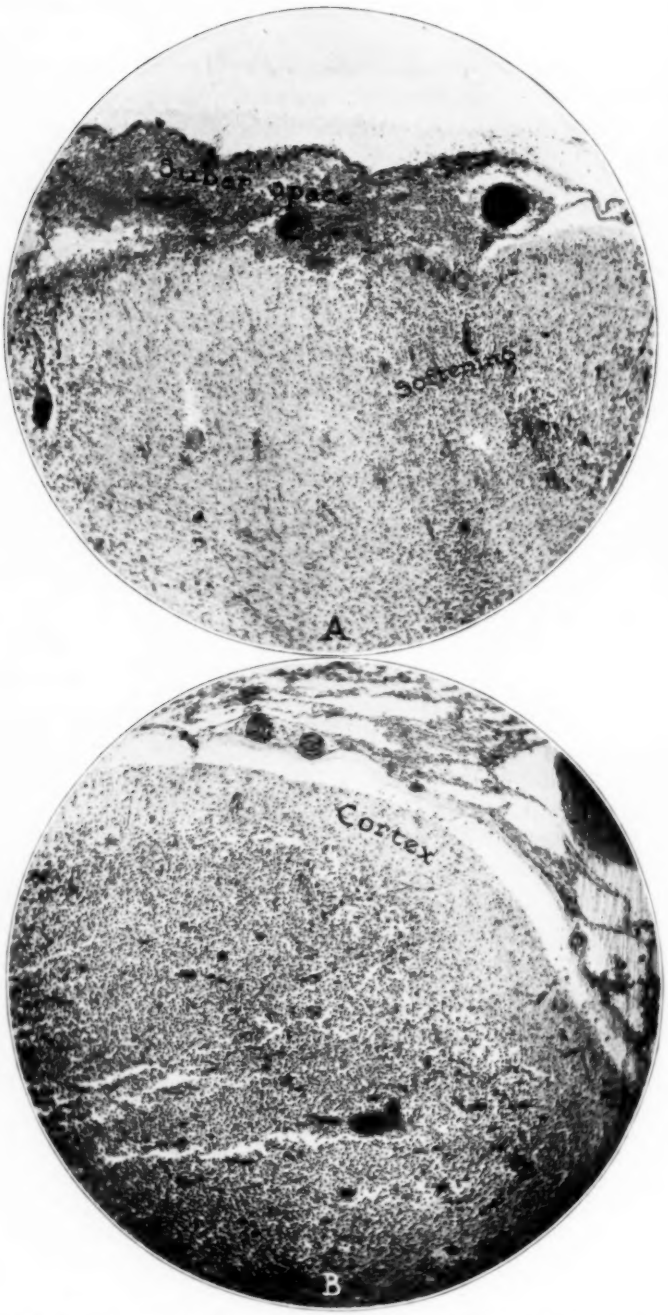

Fig. 15.—Cerebral softening: At *A* the infiltrated subarachnoid space is divided from the focus of softening in the cortex by fairly normal tissues; at *B* between the normal cortex and the letter *B* below is a vast area of softening; above the cortex is the subarachnoid space containing among other cell elements gitter cells which make up the focus in the cortex. Van Gieson stain.

Figure 16, however, shows subarachnoid and meningeal changes in a case in which morphologic changes in the brain were absent. The case was one of an acute manic state which terminated fatally within a few days after great psychic restlessness. The subarachnoid space is distended; its cells are more numerous than in the normal subarachnoid and their type is also pathologic. Some cells are lymphocytes, some fibroblasts, but the majority are histiocytes and gitter cells or appear as minute, darkly stained, rod cells provided with numerous processes

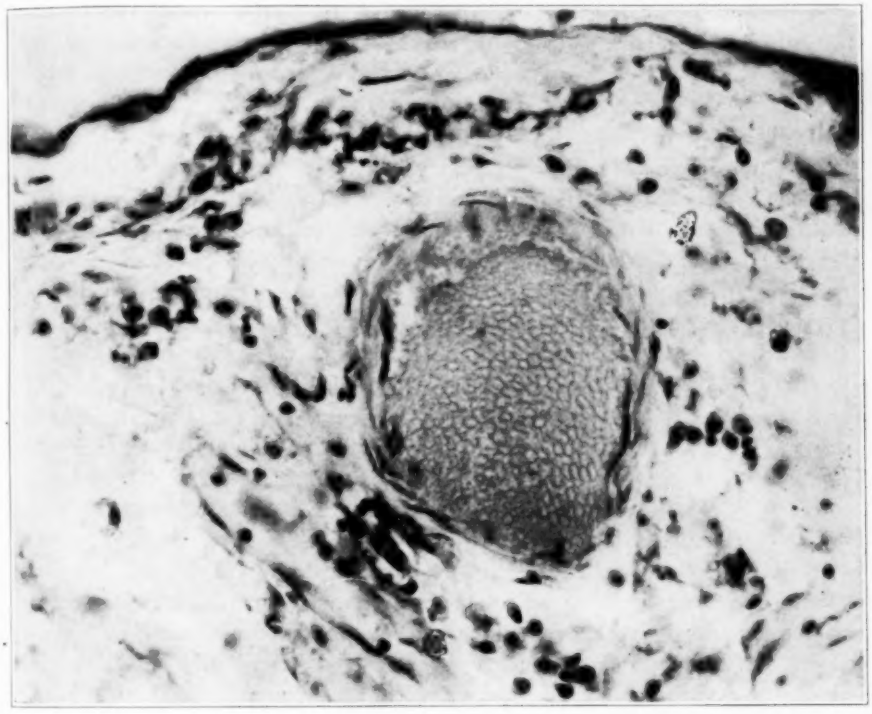

Fig. 16.—Subarachnoid space from a case of acute manic excitement. Explanations in text. Toluidine blue; × 1,000.

(not in focus). In the cerebral parenchyma they certainly would be considered to be Hortega cells. All the foregoing cells are mixed with mesothelial cells, mostly in the form of dense foci (clusters). The trabeculae are thickened, separated from one another, and form dilated meshes. The intima piae shows fibroblasts—in the form of oblong nuclei with polar processes—and very large lymphocytes with a wealth of cytoplasm and chromatin-rich nuclei. The blood vessels are patent and not infiltrated, and the endothelial as well as the adventitial cells are prominent.

In short, the reactive phenomena in the subarachnoid space, in this case of a mental disorder, differed in no way from those present in the previous instances, although the brain parenchyma showed no structural alterations. The condition may be classified as meningitis. The changes also resemble those seen in the meninges as a result of injections of indifferent substances (laked blood, lampblack) into the subarachnoid space. Such meningeal changes were termed by Ayer [13] aseptic meningitis. This type of meningitis, thus, may occur in conditions which may be termed psychic or mental. The meningitis is here caused most likely by chemical substances discharged from the brain. Were the meningitis primary, caused by the same irritants that produced the lesion of the parenchyma of the brain, the reactive phenomena, especially in the blood vessels, certainly would be much more extensive than they were found to be in my case or than are present in general in aseptic meningitis. Here the meshes of the subarachnoid spaces are distended, the trabeculae are thickened and their cell content is increased, but not to such an extent as is seen in the classic infectious types. For this reason, the aseptic forms are more suitable for the study of reactive meningeal phenomena in the intima piae—as they show in the trabeculae, mesothelial cells, histiocytes, etc.—than the infectious types, with their enormous infiltrations in which the foregoing structures are effaced. The study, for instance, of the condition of the mesothelial cells shows, in contrast to the observations of Essick,[14] Ayer, Stone [15] and others, a total indifference to the irritants that arrive in the subarachnoid space from the brain. The lack of mesothelial cell reaction is also in contrast to the reaction exhibited by lymphocytes and histiocytes, an occurrence that is of enormous importance, for it is suggestive of what takes place in the brain even in the apparent absence there of morphologic changes. It would seem that reactive meningeal phenomena (aseptic meningitis) are of much greater significance than those occurring in the classic types, and for this reason they should be studied in cases in which structural changes in the brain are in the background. It would, for instance, be of interest to observe the condition of the subarachnoid space and the meninges in various mental disorders—manic-depressive, schizophrenic and other psychotic states—with a view to determining the possible presence of meningeal reactive phenomena.

13. Ayer, James B.: A Pathological Study of Experimental Meningitis from Subarachnoid Inoculation, Monograph, Rockefeller Institute for Medical Research, 1920, vol. 12, p. 26.

14. Essick, C. R.: Formation of Macrophages by Cells Lining the Arachnoid Cavity in Response to the Stimulus of Particulate Matter, Contrib. Embryol. **9**:377, 1920.

15. Stone, T. T.: Leptomeningitis; Formation of Macrophages from Arachnoid Cells, Arch. Neurol. & Psychiat. **23**:106 (Jan.) 1930.

As I have pointed out, these are as yet the only histologic means of ascertaining what is going on in the brain in some uncertain or doubtful pathologic conditions.

CONCLUSIONS

1. Meningitis is a collective name for reactive histologic phenomena in the cerebral meninges against an infection or an intoxication.

2. The reaction is displayed by the various cell bodies, hematogenous or histogenic, that are normally present in the meninges and the subarachnoid spaces.

3. The mesothelial cells may react by proliferation, but generally their morphology remains unchanged. Their rôle is mainly passive.

4. Aside from the well established infectious types of meningitis, a noninfectious or aseptic type should be considered.

5. The meningeal reaction in the aseptic type of meningitis is similar to that produced experimentally—by the subarachnoid injection of laked blood, lampblack and similar products.

6. Aseptic meningitis may be in evidence even in cases in which no structural changes in the brain are present; it is a result of the action of chemical substances discharged by the brain into the subarachnoid space.

7. The overcrowded subarachnoid space reflects on the parenchyma of the brain and cord by causing a distention of the tissue spaces and their rarefaction or areolar appearance.

8. The cerebral tissue and perivascular spaces form with the subarachnoid space one continuous system. A lesion of one portion affects, to a certain extent, the rest.

INFLAMMATORY DISEASE OF THE CENTRAL NERVOUS SYSTEM

SO-CALLED NONSUPPURATIVE ENCEPHALITIS AND ENCEPHALOMYELITIS

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NEW YORK

The problems concerning the causation and the distinctive morphologic features of the several forms of nonsuppurative disease of the central nervous system, though recently subjected to searching investigations, are still awaiting solution. The efforts in this direction continue to be blocked, primarily by the failure to find the causative agent of the disease in question, and are in large measure retarded by the lack of full agreement among morphologists in the interpretation of the basic phenomena that underly the conception of inflammation. It is obvious that terms such as encephalitis, encephalomyelitis and similar designations, adapted for inflammatory diseases in the various subdivisions of the central nervous system, are of doubtful service without a precise knowledge of what constitutes inflammation. They will remain so, unless the morphologic symptom complex of the so-called inflammatory disease of the central nervous system is clearly defined. The conflicting views held by various schools, led by Marchand,[1] Aschoff,[2] Lubarsch,[3] Fischer-Wassels [4] and others,[5] with regard to the conception of inflammation

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From the Laboratories of the Mount Sinai Hospital and the Deutsche Forschungsanstalt für Psychiatrie, Kaiser Wilhelm Institut, Munich, Germany.

1. Marchand, F.: Lehre von der Entzündung, in Krehl, L., and Marchand, F.: Handbuch der allgemeinen Pathologie, Leipzig, S. Hirzel, 1924, vol. 4.

2. Aschoff, L.: Zur Begriffbestimmung der Entzündung, Beitr. z. path. Anat. u. z. allg. Path. **68**:1, 1921; Ueber die Einteilung der Krankheiten des Nervensystems, ibid. **71**:19, 1923.

3. Lubarsch, O.: Referat über die Entzündung, Verhandl. d. deutsch. path. Gesellsch. **19**:3, 1923.

4. Fischer-Wassels, B.: Der Entzündungsbegriff, Munich, J. F. Bergmann, 1924.

5. Rössle, R.: Referat über Entzündung, Verhandl. d. deutsch. path. Gesellsch. **19**:18, 1923. Borst, M.: Ueber Entzündung und Reizung, Beitr. z. path. Anat. u. z. allg. Path. **63**:633, 1917.

have aimed at a removal of the limitations placed about it by the older anatomists and have brought some confusion into the field of neuropathology. Disturbing as this may be, it has stimulated newer investigations and provoked valuable discussion that has resulted in a clearer restatement of views with regard to the biologic significance of the morphologic alterations that occur in inflammation.

Fortunately, agreement has been reached in some points; among these is the recognition of inflammation as a defensive reaction on the part of the organism, in which the local vascular and supporting tissue components of the involved organ or region are mobilized to ward off, to destroy the invading disturber or to neutralize its effects and to protect the contiguous uninvolved tissue. But in the application of this conception, more particularly to inflammation occurring in the central nervous system, it became necessary to make a distinction between two closely related phenomena, inflammatory disease and inflammatory reaction. Under the former is now understood an essential or primary disease process which, though bearing strong similarity to the secondary, so-called reactive inflammation, occurs as an isolated disease process independent of other coexisting lesions. Indeed, it includes all the anatomic alterations that characterize the inflammatory reaction to be defined in the course of this paper, but, in addition, consists also of other structural changes, which punctuate the course of the disease from its incipiency throughout its various progressive or regressive stages, till it either terminates by healing or complete dissolution or is interrupted by a fatal issue. Thus, in inflammatory disease there may be encountered some or all of the three phenomena constituting the triad of morphologic symptoms essential to inflammation: the exudative, proliferative and alterative. On the other hand, the condition that is now designated as inflammatory reaction represents only one phase of the inflammatory disease, but it often assumes a subordinate position and under unusual circumstances may be totally absent.

The distinction between inflammatory disease and inflammatory reaction is particularly important in neuropathology, and its significance becomes more apparent when it is recalled that morphologic features of the inflammatory reaction may often occur in association with conditions that are unquestionably noninflammatory, as seen in the frequent appearance of adventitial infiltration in nerve tissue adjoining a neoplasm, or adjacent to an area of necrobiosis caused by circulatory disturbances. Useful as it is, the distinction between the inflammatory disease and its main anatomic landmark—the inflammatory reaction—is often not very clear, and a decision may be reached only when the provocative agent is identified and the existence of an infectious process is established, or when the finding of a noninfectious cause, such as a necrobiotic process due to vascular disturbances or provoked by a neoplasm, excludes the

existence of an infectious agent and establishes the secondary or reactive character of the alterations. The tempo with which an inflammatory reaction is developed is another important aid in the evaluation of the nature of the process. A defensive inflammatory reaction in response to an invading organism, as in pure inflammatory disease, evolves rapidly in the early stages of the disease; under other circumstances it is marked by a gradual evolution and in the majority of instances is found to be accompanied by a visible, distinctly noninfectious causative factor. For the present the useful and well grounded distinction between the inflammatory disease and inflammatory reaction may be accepted, and the discussion of the morphologic features of inflammatory disease in the central nervous system, often referred to as the encephalitic symptom complex or as primary encephalitis (Spielmeyer [6] and Spatz [7]), may be undertaken.

Spielmeyer,[6] following the lead of Nissl,[8] in order to meet the urgent and practical needs in neuropathology, has presented a comprehensive and workable formula. Its value is to be found in the fact that it takes cognizance of the morphologic manifestations peculiar to inflammatory diseases of the central nervous system. It reserves the term encephalitis as a designation for a disease entity and rescues it from an evergrowing inflation, which is provoked by the broad interpretation of the biologic principles involved in the conception of inflammation. In accord with the older concepts, it provides a dominant rôle for the alterations displayed by the mesodermal components of the vascular and supporting connective tissue apparatus in the encephalitic symptom complex.

These alterations manifest themselves in what is commonly known as cellular infiltration and is referred to as perivascular or advential infiltration. The term cellular infiltration, when applied to the central nervous system, is restricted to the local collections of liberated or migrated mesodermal elements aggregating in the immediate vicinity of blood vessels and in the leptomeninges of the central nervous system. The term infiltrating cell is assigned to mobile cell forms, such as the polymorphonuclear leukocytes, lymphocytes, small and large and their derivatives, plasma cells, mast cells and macrophages (fig. 1). The latter, in the form of compound granular cells, which are often inter-

6. Spielmeyer, W.: Histopathologie des Nervensystems, ed. 1, Berlin, Julius Springer, 1922.

7. Spatz, Hugo: Encephalitis: Die Anatomie der Psychosen, in Bumke, Oswald: Lehrbuch der Geisteskrankheiten, Berlin, Julius Springer, 1930, vol. 7.

8. Nissl, F.: Die Histopathologie der paralytischen Rinderkrankung, Histologische und histopathologische Arbeiten über die Grosshirnrinde, Jena, Gustav Fischer, 1904, vol. 1, p. 315.

mixed with other infiltrating elements, because of their doubtful origin are not grouped with the cells typifying an inflammatory disease or reaction.

Though I am not particularly concerned here with the origin of the infiltrating cells, brief reference to the views held as to their derivation may not be out of place. A division of opinion still exists as to whether these cellular elements migrate out of the blood stream into the adventitial spaces and then, at times, into the extravascular territory, or whether they arise in situ from the endothelial components of the adventitial cells of the blood vessels. Accumulating evidence favors

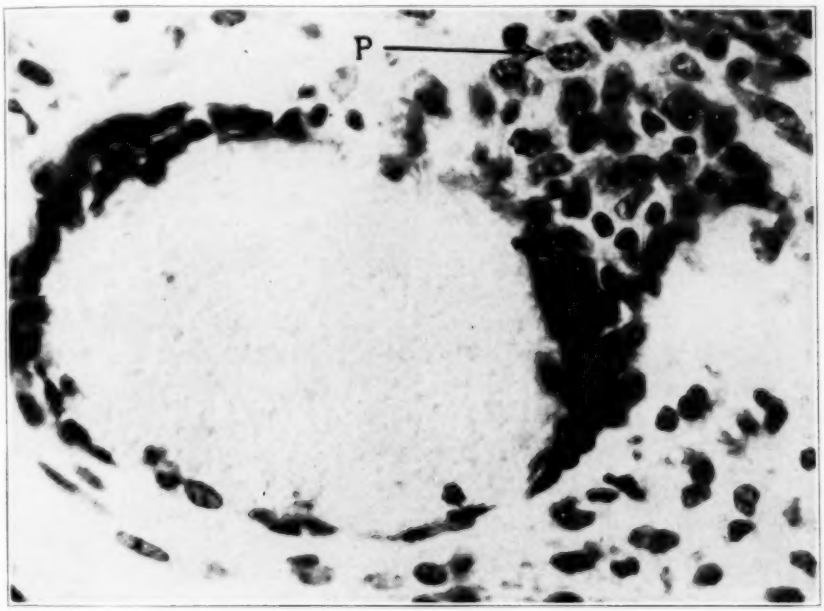

Fig. 1.—Adventitial and extravascular infiltration in encephalomyelitis postvaccinalis, showing the large number of plasma cells (*P*). Nissl stain.

the former concept. Recently, Michels and Globus[9] were able to demonstrate in polio-encephalitis, encephalomyelitis, acute epidemic encephalitis and various forms of syphilis of the central nervous system (fig. 2) a process of active migration of lymphocytes through the vessel wall into the adventitial space and then beyond it into the extravascular territory. These observations gained additional significance

9. Michels, N. A., and Globus, J. H.: The So-Called Small Round Cell Infiltrations: I. Polio-Encephalitis and Acute Epidemic Encephalitis, Arch. Path. **4**:692 (Nov.) 1927; II. Syphilis of the Central Nervous System, ibid. **8**:371 (Sept.) 1929.

from the fact that no evidence was revealed in favor of the claim that fixed endothelial cells metamorphose into infiltrating cells. This, of course, is in accord with the teaching of Maximow [10] and Nissl; it is out of accord with the views of Marchand [11] and von Möllendorff,[12] who assigned the origin of a large portion of the infiltrating cells to fixed adventitial structures. Michels and Globus were also able to demonstrate the gradual transition of lymphocytes into plasma cells and mast cells, thus substantiating the views held by Nissl [8] and others.

Fig. 2.—Fossilized migrating lymphocytes in dementia paralytica. Maximow stain.

It must be borne in mind, however, that in spite of the fact that the so-called perivascular infiltration is a morphologic feature that

10. Maximow, A. A.: Experimentelle Untersuchungen über die entzündliche Neubildung von Bindegewebe, Beitr. z. path. Anat. u. z. allg. Path. **32**:1, 1902; Untersuchen über Blut und Bindegewebe, Arch. f. micr. Anat. **73**:444, 1909; **77**:1, 1910; **96**:494, 1922; Morphology of the Mesenchymal Reactions, Arch. Path. **4**:557 (Oct.) 1927.

11. Marchand, F.: Ueber die Herkunft der Lymphozyten und ihre Schicksale bei der Entzündung, Verhandl. d. deutsch. path. Gesellsch. **16**:5, 1913.

12. von Möllendorff, W.: Die örtliche Zellbildung im Gefässwänden und im Bindegewebe, München. med. Wchnschr. **74**:135, 1927.

dominates the picture of inflammatory disease and is almost pathognomonic of essential encephalitis, one must be exceedingly careful in its evaluation, for, as already noted, it also serves as the main expression of so-called inflammatory reaction in noninfectious diseases of the central nervous system.

A second important morphologic symptom that is regularly found in inflammatory disease of the central nervous system consists of the changes displayed by the neuroglia. Until recently, glial activity was regarded as a secondary reactive phenomenon. But it is now agreed that despite the fact that the neuroglia, in common with the nerve parenchyma, is of ectodermal origin, it is little more than a special form of supporting tissue peculiar to the central nervous system. It serves the central nervous system in the same capacity as the supporting tissue of mesodermal origin in other organs. It parallels it in almost every way. Physiologically, it assumes a phagocytic function in a manner similar to that of the phagocytes of mesodermal derivation. Morphologically, it serves as supporting tissue, and shares with the mesodermal derivatives in the production of compound granular cells.

What is still more significant is that in the microglia, a special form of neuroglia, there is found an important connecting link between these two varieties of supporting tissue. In fact, there is now a strong tendency in the direction of assuming a mesodermal origin for the microglia, which for this reason are often referred to as mesoglia. The staining reaction of these cells is much like the staining affinities of reticulo-endothelial cells,[13] the phagocytic character being common to both the microglia and the reticulo-endothelial structure. These similarities are utilized as strong arguments in favor of their common mesodermal derivation. However, the occurrence of large numbers of these cells, the derivation of which is still somewhat obscure, in inflammatory disease is now accepted as a more or less constant feature in essential encephalitis. Nissl, who was first to identify them, naming them *Stabchenzellen* (rod cells), was firm in the belief that they play a conspicuous rôle in the morphologic symptom complex of dementia paralytica, a disease process now definitely recognized as a form of encephalitis. More recently, Spielmeyer[14] showed that microglia, constituting the so-called glia nodules (fig. 3), occur regularly as an associated or independent morphologic symptom of inflammatory disease. It is often said that their frequent conversion into compound

13. Belezky, W. K.: Die Pyridinsodamethode zur Imprägnation der Mesoglia (Hortegazellen, Oligodendroglia, Drenagzellen) und Reticuloendothelzellen (für Gelatin- und Celloidinschnitte), Virchows Arch. f. path. Anat. **282**:214, 1931.

14. Spielmeyer, W.: Die zentralen Veränderungen beim Fleckfieber und ihre Bedeutung für die Histopathologie der Hirnrinde, Ztschr. f. d. ges. Neurol. u. Psychiat. **47**:1. 1919.

granular cells excludes them as participants in inflammatory disease. It is true that, as they acquire the character of phagocytes (compound granular cells—fig. 4), they are mainly concerned with reabsorption of products of dissolution, but this should not detract from the rôle they play in inflammation, as it only shifts their position from the exudative to the reparative stages in the inflammatory disease. However, the participation of compound granular cells of whatever derivation, lymphocytic or glial, in the early stages of inflammation is now accepted as probably a direct response to the initial irritation, and hence

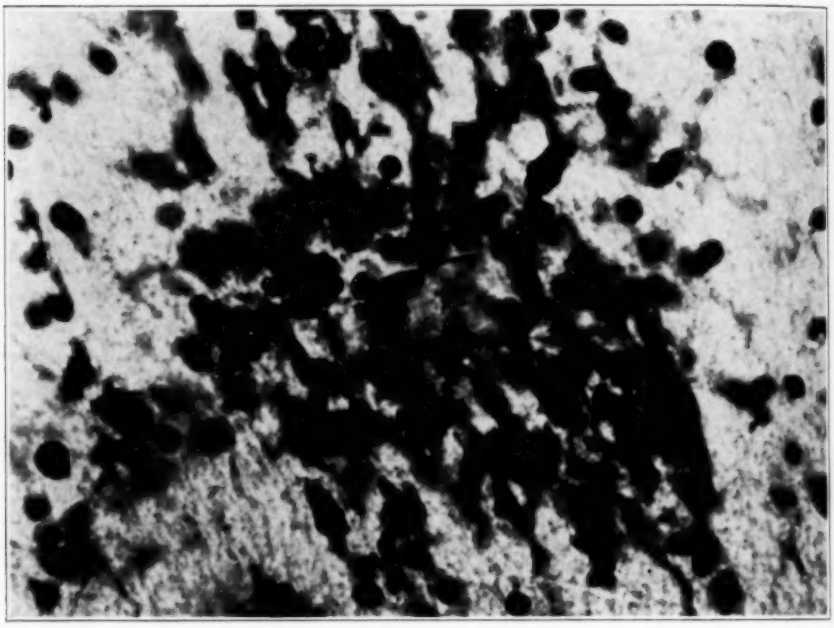

Fig. 3.—Glial nodule, consisting of microglial elements. Nissl stain.

their presence does not vitiate the modern conception of inflammatory disease in the central nervous system.

Spielmeyer [15] insisted on the capacity of glial elements to become activated not only in reaction to accumulated products of dissolution, which assume the character of foreign bodies, but also in direct response to irritation by a noxious agent. Glial aggregations of various types, particularly those described by Spielmeyer and later by Scholz [16] and

15. Spielmeyer, W.: Infektion und Nervensystem, Ztschr. f. d. ges. Neurol. u. Psychiat. **123**:161, 1930.

16. Scholz, W.: Herdförmige, protoplasmatische Gliawucherungen von syncytialem Charakter: Ausblick auf Bedeutung für den Verlauf des pathologisch-anatomischen Prozesses bei der Encephalitis epidemica, Ztschr. f. d. ges. Neurol. u. Psychiat. **79**:114, 1932.

others, have been observed early in well established inflammatory diseases of the brain, in instances in which the conventional landmarks of such disease, the mesodermal inflammatory reactions, have not been revealed. This testifies to the capacity of the glia to react without provocation by necrobiotic products in the initial stages of inflammatory disease.

It is obvious from the foregoing that the inflammatory disease is marked by activation of both the mesodermal and the glial components of the central nervous system. Indeed, the admission of the glial elements as participants, and even as independent factors, in an inflammatory process tends to lower the partition between essential inflammatory

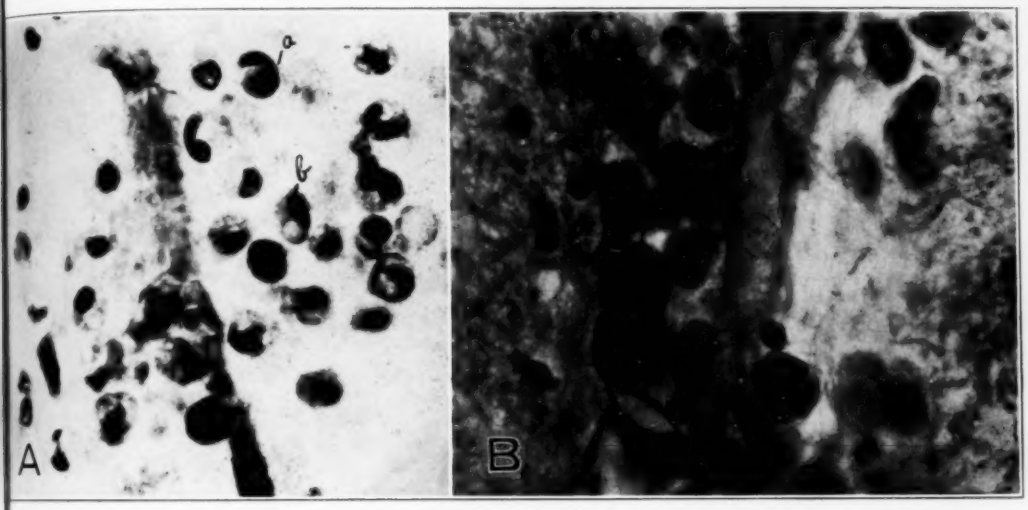

Fig. 4.—Compound granular cells: *A*, of lymphocytic origin; *a*, and *b*, typical cells; *B*, of glial origin.

disease and disease conditions regarded as degenerative or often ambiguously labeled as toxic-inflammatory under terms such as toxic encephalitis, encephalosis or degenerative encephalopathy. Under such circumstances the formula of Spielmeyer, in its aim to identify inflammatory disease of the nervous system, is in grave danger, and its full value can be maintained only if one can establish a direct relationship between infection and inflammatory disease and clear the field by excluding conditions distinctly noninfectious in character.

To meet such needs, Spatz [17] formulated several questions that, on a critical analysis, he answered fully and satisfactorily, concluding

17. Spatz, Hugo: Ueber Encephalitis und Encephalitiden, Nervenarzt **4**:466, 1931.

that infection of the central nervous system, with but few exceptions, provokes the morphologic syndrome of inflammatory disease and that essential inflammatory disease is always caused by infection. To answer more adequately the first question—i. e., whether inflammatory disease may occur in the central nervous system without infection—he qualifies and defines the term as an invasion by foreign bodies in the form of micro-organisms or an ultramicroscopic virus, with subsequent spread through the parenchyma. The finding of such bodies in the

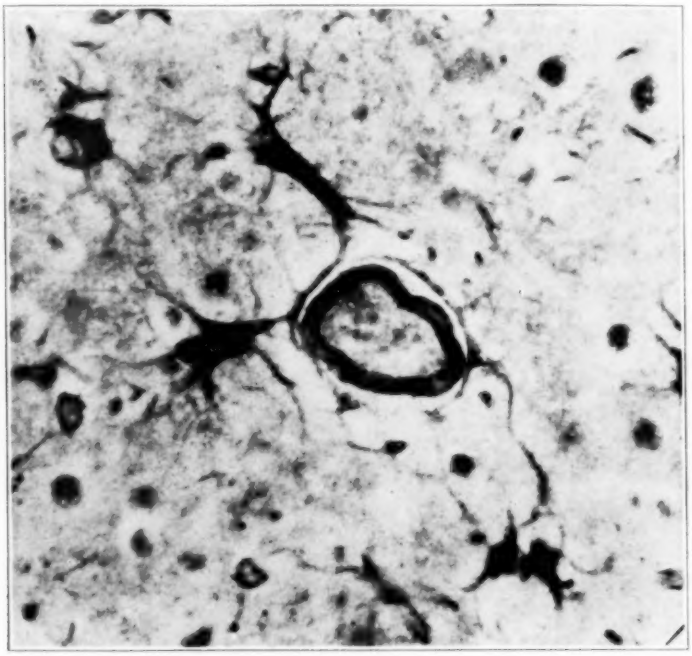

Fig. 5.—Membrana limitans gliae. Globus modification of Cajal's gold sublimate method.

blood circulating through the central nervous system is for obvious reasons not accepted as evidence of their presence in the parenchyma. The central nervous system, thanks to a structural peculiarity, is provided with a protective mechanism that walls off the ectodermal components from its vascular apparatus. This limiting glial membrane (fig. 5), in conjunction with the adventitial wall of the blood vessels, is a strong line of defense that prevents the entrance of noxious foreign bodies freely circulating in the blood stream or in the subarachnoid space into the contiguous nerve tissue.

Hence the often quoted views of Fraenkel[18] that infection of the central nervous system may exist without manifest inflammatory disease, when critically analyzed, fail to detract from the position held by Spielmeyer and Spatz, that infection in nerve tissue almost always causes an inflammatory reaction. To repeat, the fact that organisms can be obtained from preparations or cultures of nerve tissue does not prove their presence in the parenchyma of the organ, for they may have been recovered from the blood stream of the organ. In fact, it would be rather surprising in conditions of generalized sepsis to find the cerebral blood sterile. The frequent failure of organisms circulating in the blood to penetrate into the parenchyma is a fortunate circumstance and is due to the existence of the already mentioned additional line of defense peculiar to the central nervous system. It is only when this defense fails, probably because of a lowering of local resistance, that organisms invade the parenchyma. In that event the unfolding of the picture of pure inflammatory disease is almost certain.

There are, of course, exceptions to this rule, and instances are met in which, because of the high virulence of the invading organism or because of the lowered local immunity, the clinical course assumes a fulminating character, terminates early in a fatal issue and thus precludes the evolution of the defensive reaction (Globus and Strauss[19] and Spatz[17]). The so-called acute serous encephalitis of Brown and Symmers,[20] assumed to be a separate form of encephalitis, can now in the light of the foregoing conception be regarded as an inadequate inflammatory response of the nerve tissue to overwhelming infection, as testified by the fulminating clinical course typical of those cases. This may also hold true of the toxic encephalitis of Grinker and Stone.[21] There, also, the explosive onset, the rapid clinical course and the rapid fatal termination indicate that the lethal character of the noxious agent eluded every attempt at a typical inflammatory reaction. This view finds its support in the emphasis placed by Grinker and Stone on the advanced pathologic alterations in the vascular apparatus. On the other hand, there are instances in which the virulence of the organism is very low or the local immunity is sufficiently high to ward off the invader without displaying a fully developed inflammatory reaction, so that no frank

18. Fraenkel, E.: Ueber das Verhalten des Gehirns bei akuten Infections-Krankheiten, Virchows Arch. f. path. Anat. **194**:168, 1908.

19. Globus, J. H., and Strauss, Israel: Subacute Epidemic (Lethargic) Encephalitis, Arch. Neurol. & Psychiat. **8**:122 (Aug.) 1922.

20. Brown, C. L., and Symmers, Douglas: Acute Serous Encephalitis, Am. J. Dis. Child. **29**:174 (Feb.) 1925.

21. Grinker, R. R., and Stone, T. T.: Acute Toxic Encephalitis in Childhood: A Clinicopathologic Study of Thirteen Cases, Arch. Neurol. & Psychiat. **20**:244 (Aug.) 1928.

manifestations of inflammations are discernible. With these two exceptions, infections of the central nervous system lead to the morphologic alterations typifying inflammatory disease.

The other question bearing on the same general problem, whether inflammatory reaction may occur without existing infection, has already been partly answered. It is common experience to find circumscribed inflammatory reactions in areas of aseptic damage to the brain due to violence or local necrobiotic processes, as in softening due to circulatory disease or as in the devitalized tissue bordering on cerebral neoplasms. But in such instances the gross lesions provoking such inflammatory reaction are easily recognized, and the restricted character of the reaction is also indicative of the secondary character of such reactions. They are provoked by massive liberation of endogenous products, which act as foreign bodies. It is rather noteworthy that these phenomena occur only during the active process of disintegration, and as the latter slows up or dies out the reactive changes disappear.

A thorough purgation of the term encephalitis demands also a clear answer to the question as to whether toxins are capable of producing inflammatory disease, as is apparently assumed by those who chose the terms toxic encephalitis and toxic myelitis to designate such conditions. The answer, which is, of course, in the negative, may be drawn from the behavior of tetanus toxins endowed with a selective action on the central nervous system. Repeated investigations and recently my own experience with a fatal case have failed to reveal an inflammatory process in the central nervous system of persons who died of tetanus intoxication. This is but one of many examples in which the clinical picture of toxic encephalitis is not accompanied by morphologic evidence of inflammatory disease, aside from regressive changes in the parenchyma and some activation of the neuroglia, mainly that of the oligodendroglia variety. The obviously misleading nature of the term toxic encephalitis is further illustrated also by the so-called arsphenamine encephalitis, in which all the morphologic manifestations of inflammatory disease are lacking, and purely disruptive changes in the vascular apparatus with mild reactive changes in the glia are present (fig. 6). Alcohol, in its selective action on the central nervous system, is known to produce local disturbances in the brain stem, which are often labeled "polio-encephalitis haemorrhagica superior," without substantiating morphologic evidence of an inflammatory process aside from productive changes in the walls of the blood vessels. The so-called lead encephalitis is another example of the misuse of the term encephalitis (Hassin [22]).

22. Hassin, G. B.: The Contrast Between the Brain Lesions Produced by Lead and Other Inorganic Poisons and Those Caused by Epidemic Encephalitis, Arch. Neurol. & Psychiat. **6**:268 (Sept.) 1921.

With the foregoing in mind, it is possible now to free the term encephalitis from its contaminants by excluding a large group of non-infectious disturbances in the brain, which clinically simulate the picture of encephalitis, and by assigning them temporarily to a group for which Spatz suggested the name of pseudo-encephalitis. In this manner one may restrict the term encephalitis to inflammatory diseases of the brain, of infectious origin, no matter whether or not the infectious agent is identified.

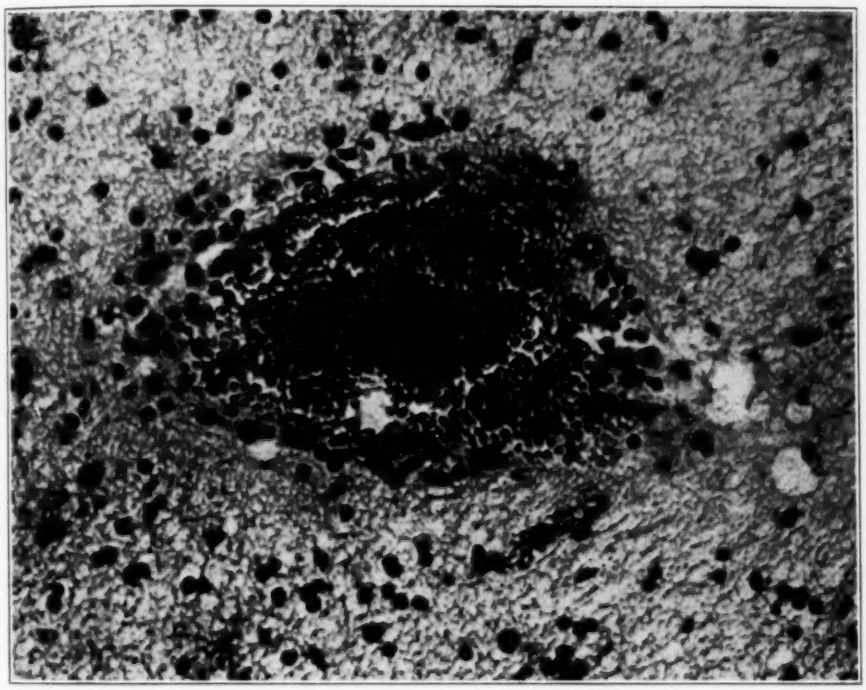

Fig. 6.—Disruption of vessel wall and extravasation of blood elements. Arsphenamine pericapillary encephalorrhagia. Globus modification of silver carbonate method of Hortega.

THE ESSENTIAL ENCEPHALITIS AND ENCEPHALOMYELITIS

There are several forms of primary or essential inflammatory disease of the central nervous system, which are clinically identified as distinct types. Among them one finds: (1) polio-encephalitis of the Heine-Medin type, with its homolog, poliomyelitis; (2) acute epidemic encephalitis, von Economo's disease; (3) rabies encephalitis (encephalitis-Lyssa); (4) postvaccinal encephalitis and the related postinfectious encephalitides; (5) acute disseminated encephalomyelitis, with the closely related condition, described under the name of multiple sclerosis; (6) the

encephalitis periaxialis diffusa of Schilder, or the diffuse sclerosing encephalitis of Spielmeyer [23] and (7) the syphilitic forms of encephalitis, which are not included in this discussion. All of the enumerated forms of encephalitis or encephalomyelitis conform in some of their morphologic features to a central type that meets, in the main, the demands imposed by the definition of essential encephalitis. But they also present wide deviations and variations in their clinical pictures, which justify attempts to distribute them into separate groups. The task, however, is difficult. In the absence of precise knowledge of the causative factor, with the nonspecifity of the inflammatory reaction, and because of the lack of sharp lines of demarcation between the several forms, the time is not ripe for scientifically sound classification.

However, the temptation is great to contribute something definite to the solution of this problem, and thus, among others, Pette [24] and more recently Spatz [7] have presented schemes for the classification of the encephalitides. Pette, accepting the views of Levaditi [25] and his pupils as already established facts, assumed that in the large group of the so-called nonsuppurative encephalitides there is an inflammatory process provoked by a filtrable virus, the latter occurring in various strains grossly divisible into the two main varieties: those that attack selectively the gray and those that attack predominantly the white substance of the central nervous system. This hypothesis forms the basis for a plausible, but as yet not acceptable, classification of the encephalitides. Accordingly, Pette spoke of encephalitides and encephalomyelitides, in which the disease is predominantly that of the gray substances, and those in which the disease is limited to, or more extensive in, the white matter. Under the former he named (1) polio-encephalitis of the Heine-Medin type, (2) acute epidemic encephalitis of von Economo and (3) the experimentally produced herpes encephalitis. Under the second group he listed (1) postvaccinal encephalitis and its homologs, acute disseminated encephalomyelitis, including also acute multiple sclerosis. There is here an attempt by still uncertain and debatable data pertaining to the etiology and pathogenesis of the diseases in question and by fortifying them with somewhat less questionable morphologic observations to map out a plan for the grouping of the encephalitides.

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23. Spielmeyer, W.: Der anatomische Befund in einen zweiten Fall von Pelizaeus Merzbacherschen Krankheit, Zentralbl. f. d. ges. Neurol. u. Psychiat. **32**:203, 1923.

24. Pette, H.: Infektion und Nervensystem, Deutsche Ztschr. f. Nervenh. **110**: 221, 1929.

25. Levaditi, C.: Ectodermoses neurotropes, Paris, Masson & Cie, 1922; Etiology of Epidemic Encephalitis: Its Relation to Herpes, Epidemic Poliomyelitis Postvaccinal Encephalopathy, Arch. Neurol. & Psychiat. **22**:767 (Oct.) 1929.

The entire structure of Pette's scheme and its modifications falls to the ground if one agrees with some or all of the objections that Spielmeyer [15] raised against its underlying conceptions. To begin with, the distinction between the pathogenesis of suppurative and that of nonsuppurative diseases of the central nervous system is not as clearcut as has been assumed by Pette, who, drawing too sharp a line of demarcation between them, utilized insecure histologic data as means for identification of the character of the causative agent. To follow Pette, one must agree with him that polymorphonuclear leukocytic infiltrations are always provoked by a bacterial invasion, and that small lymphocytic infiltrations regularly indicate an invasion by a filtrable virus. It is now well recognized that in infection of the central nervous system in which, so far, no visible or known micro-organism has been disclosed, though the disease, as assumed on good grounds, is very likely provoked by a virus, polymorphonuclear leukocytes appear uniformly in varying numbers in the early stages of the disease. It is likely that they serve in the important capacity of phagocytes and digesters of invaders. However, their early disappearance and replacement by mononuclear elements has often led to erroneous deductions and to the assumption that polymorphonuclear infiltrations serve to uncover and to identify the invaders as a coarser micro-organism, and that they do not participate in the inflammatory reaction provoked by a filtrable virus. It is obvious that their presence, though only at one stage of the disease, wipes out the sharp line of division between the suppurative and nonsuppurative diseases of the central nervous system unless there are other factors that aid in making this distinction, such as the presence of a focus of massive suppuration.

The acceptance of the view that there are two main groups of filtrable neurotropic viruses, with selective tendencies or tropisms, is still somewhat premature, for they are supported by morphologic data that are still under discussion. Numerous examples may be cited of well established instances of polio-encephalitis or poliomyelitis in which the white substance participates equally with the gray in the disease process. The reverse is also true, as in postinfectious encephalitis (fig. 7), acute multiple sclerosis and acute disseminated encephalomyelitis, in which the gray matter shares equally or carries the brunt of the pathologic process.

Spatz, utilizing the results of his own investigations on the distribution of dyes [26] injected into the subarachnoid system and amplifying them with the known facts of the distribution of lesions in the various

26. Spatz, H.: Versuche zur Mitzbarmachung des E. Goldmannsche vital Farb-Stoffversuche (die Trypanblau Meningitis), Allg. Ztschr. f. Psychiat. **80**:285, 1924-1925.

forms of inflammatory disease of the central nervous system, offered another plan for their classification. Inclined to the view that a mechanical factor determined the portal of entry of the inciter and the channels of its transmission, acting in conjunction with several other less clearly understood factors, such as local circulatory peculiarities stressed by Spielmeyer, the degree of virulence of the invading agents and the state of local tissue resistance or local vulnerability, he proposed to distribute the encephalitides into the following groups: (1) meningo-encephalitis, (2) metastatic encephalitis, (3) the confluent form of encephalitis, (4) polio-encephalitis of the patchy type, exemplified by

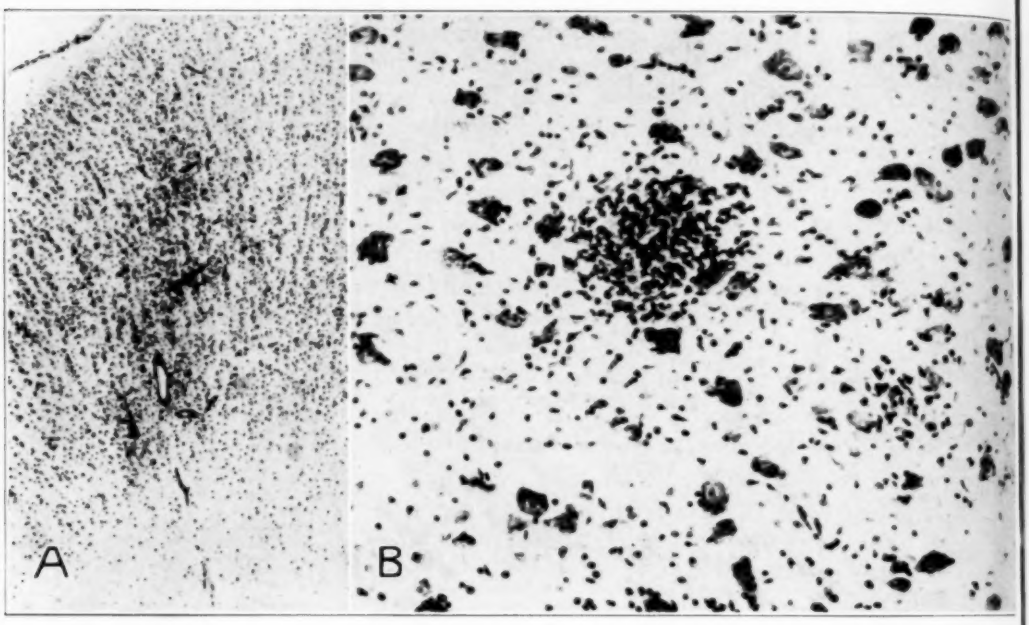

Fig. 7.—*A*, intensive inflammatory alterations in the gray substance in measles encephalomyelitis. *B*, glial (microglial?) nodule in typhus encephalitis. Nissl stain.

acute epidemic polio-encephalitis and acute epidemic encephalitis, (5) acute disseminated demyelinizing and acute epidemic encephalomyelitis or acute multiple sclerosis and (6) acute perivenous encephalitis (post-vaccinal encephalitis and its homologs).

It is realized that this scheme does not yet satisfy fully the demands, but as it does not outrun the few known and firmly established facts it is less objectionable. Though I am primarily concerned with the last three groups, interest is to some extent also claimed by the first three groups, for they present characteristic morphologic patterns that mirror well recognized modes of invasion and diffusion of the noxious agents.

and hence may throw light on some factors that are instrumental in the distribution of inflammatory reactions in the less clearly understood forms of encephalitis and encephalomyelitis.

1. *The Meningo-Encephalitic Groups.*—These illustrate well how an infectious agent, having entered a peripheral extension of the subarachnoid space, rapidly reaches the main reservoirs and then spreads through their distributing channel on the inner and outer surfaces of the brain. The origin of this form of inflammatory disease is commonly traced to organisms harbored in an infectious focus, in direct proximity to the leptomeninges or to a vessel passing through the pia-arachnoid space. By virtue of this contiguity, the organisms find easy access to some part of the pia-archnoid space with consequent diffusion along certain regular channels. Spatz' experimental studies on the mode of distribution of dyes in the cadaver or experimental animal have led him to conclude that the subarachnoid space consists of two poorly connected systems, and that this division of lack of free communication constitutes a highly important mechanical factor that determines the extent and topographic distribution of the invaders, as well as the extent and distribution of the inflammatory reactions. His views do not find full support in some observations I have made in the course of studies on communicating hydrocephalus,[27] and cannot be accepted as conclusive evidence of the dominance of the mechanical factor operative in the distribution of the lesion. That some biologic phenomena must also play an important rôle in shaping the mode of distribution is seen in the fact that, though the infection is active in the wide open subarachnoid space, it does not spread very rapidly by way of its finer ramifications throughout the brain substance in the geographically related areas. But, whatever the explanation, it is highly significant that with the noxious agent circulating in the subarachnoid space the inflammatory process is limited to the meninges, ependymal lining and to but short extensions in adjacent brain substance. This peculiarity, which distinguishes it from other forms, should be borne in mind when the morphologic manifestations of experimentally induced encephalitis are evaluated.

2. *The Metastatic or Embolic Type of Encephalitis.*—This group is well understood and engages attention here mainly because it includes instances that demonstrate the need of great caution in drawing too fine a line of demarcation between suppurative and nonsuppurative encephalitis. This is particularly true of instances in which the process has acquired a subacute character. There, the dominance of poly-

27. Globus, J. H.: Communicating Hydrocephalus, Am. J. Dis. Child. **36**:680 (Oct.) 1928.

morphonuclear leukocytic infiltration is gradually lost and the place of the cells is taken by mononuclear mesodermal derivatives and by actively proliferative microglia. The latter may make their appearance early in the disease process, and at times the glia reaction may be, as shown by Spielmeyer, the only visible response to a local accumulation of organisms, as in typhus (fig. 7 *B*).

3. *The Confluent Form of Encephalitis.*—This group is exemplified by the encephalitic process that typifies dementia paralytica. The confluency of the inflammatory process, its predominance in the gray matter and its predilection for or restriction to certain larger cerebral territories are well known and need not be discussed here. It is also not necessary to recount in greater detail certain characteristics, such as the proliferation of the microglia, their impregnation with iron, the generalized gliosis and direct relationship between the distribution of the spirochetes and the inflammatory reaction. But what is not so widely known is the occurrence of a demyelinizing process in dementia paralytica. This is important in establishing the degree of specificity of the demyelinizing process, which accompanies several of the newly studied forms of encephalitis. These areas of demyelinization, as pointed out by Spielmeyer,[28] often assume the character of plaques similar to those found in multiple sclerosis. It is significant that these plaques are most commonly found in areas where the inflammatory process is most pronounced, and that the demyelinization may at times be demonstrated by means of the Marchi method, indicating its acute character. They are not of a secondary degenerative character and may be found in any part of the cerebrospinal axis, including the spinal cord.

4. *Polio-Encephalitis of Patchy Type.*—This group constitutes the main topic for discussion. Because of the characteristic distribution of the lesion it has been designated by Spatz as the patchy form. It includes, in addition to the two best known examples of this disease, the Heine-Medin and von Economo forms of polio-encephalitis, also rabies encephalitis and Borna's disease, an encephalitis occurring in horses. Despite the already expressed objection to the sharp line of division between inflammatory disease predominantly in the white matter and that predominantly in the gray substance, it must be admitted that this is a disease form in which the gray substance bears the brunt of the inflammatory process, and, hence, the term polio-encephalitis is appropriate. Aside from predilection for the gray matter, its disseminated character and its selectivity for axial gray substances distinguish the polio-encephalitis of either the Heine-Medin or the von Economo type from the forms in the groups previously dis-

28. Spielmeyer, W.: Die Bedeutung des lokalen Faktors für die Beschaffenheit der Entmarkungsherde bei multipler Sklerose und Paralyse, Arch. f. Psychiat. **74**:359, 1925.

cussed. It is common knowledge and requires but brief mention that in acute epidemic encephalitis (von Economo [29]) the disease process strikes with greater severity and constancy the midbrain, particularly the substantia nigra, the interbrain and, less severely, the gray substance about the fourth venticle, while the cerebral cortex and the spinal cord are only rarely involved. On the other hand, in polio-encephalitis of the Heine-Medin type [30] the disease, though also most pronounced in the axial gray matter, involves more constantly and with greater severity the spinal cord, hindbrain, cerebral cortex and, as is now recognized, very frequently higher segments of the brain stem, including the substantia nigra. Thus, disturbing as it may be to those who seek sharp delimitation for disease forms, evidence is now accumulating to the effect that in the latter type of polio-encephalitis the substantia nigra and hypothalamus are sufficiently often involved so that the difference in the topography of the lesions in the two types of encephalitis need no longer be considered too rigidly.

It was thought that acute epidemic encephalitis differs from Heine-Medin's disease in that the former has a long subacute phase and assumes a slowly progressive course, during which the exudative reaction is gradually replaced by alterative and reparative phenomena, while the latter is a rapidly self-limiting process. The hypothesis of autosterilization, as formulated by Landsteiner and Levaditi,[31] was called on to explain this difference. Recently, however, it was shown by Warburg [32] that a similar tendency to chronicity may be demonstrated in experimentally produced Heine-Medin's type of polio-encephalitis. Under the circumstances this distinction loses its usefulness.

In rabies encephalitis the distribution of the lesion is often found to follow the same pattern as in acute epidemic encephalitis.[33] Borna's

29. von Economo, C.: Encephalitis lethargica, Jahrb. f. Psychiat. u. Neurol. **38**:253, 1917.

30. Strauss, I.: Epidemic Poliomyelitis, Washington, D. C., Nervous and Mental Disease Publishing Company, 1910. Peabody, F. W.; Draper, G., and Dochez, A. R.: A Clinical Study of Acute Poliomyelitis, Monograph Rockefeller Institute Medical Research, 1912, no. 4.

31. Landsteiner, K., and Levaditi, C.: Étude expérimentale de la poliomyélite aiguë (maladie de Heine-Medin), Ann. Inst. Pasteur **24**:833, 1910.

32. Warburg, Bettina: Experimental Poliomyelitis: Histology of the Persistent Lesions of the Central Nervous System, Arch. Neurol. & Psychiat. **25**:1191 (June) 1931.

33. Achucarro, N.: Zur Kenntnis der pathologischen Histologie des Zentral Nervensystem bei Tollwut, in Nissl, F.: Histologische und histopathologische Arbeiten über die Grosshirnrinde, Jena, Gustav Fischer, 1909, vol. 3, p. 143. Bassoe, Peter, and Grinker, R. R.: Human Rabies and Rabies Vaccine Encephalomyelitis, Arch. Neurol. & Psychiat. **23**:1138 (June) 1930. Schukri, J., and Spatz, H.: Ueber die anatomischen Veränderungen bei der menschlichen Lyssa und ihre Beziehungen zu denen der Encephalitis epidemica, Ztschr. f. d. ges. Neurol. u. Psychiat. **97**:627, 1925.

disease [34] differs from the three other types because of the greater frequency of the involvement of the cerebral cortex, but in this respect it is closely followed by the polio-encephalitis of Heine-Medin's type.

The distinction in the geographic distribution of the lesion becomes a little more pronounced as material from older states of the disease in question are studied. Thus, the marked atrophy of the pigmented layer in the substantia nigra becomes almost specific for acute epidemic encephalitis, while the massive loss of tissue in the ventral horns of the spinal cord in polio-encephalitis of the Heine-Medin type and in the cerebral cortex in Borna's disease are outstanding features.

It is said that in such material one sees the results of a more concentrated onslaught and greater devastation in areas of predilection by a disease process that in the acute stage appears to be diffuse and less selective.

Thus a search for histologic variations in encephalitides of this group is rewarded by meager findings. In polio-encephalitis of the Heine-Medin type in the acute stage, large numbers of polymorphonuclear leukocytes form a striking and distinctive feature. To this may be added the rapidity and severity with which the inflammatory process is unfolded, the marked disturbance in the defense line provided by the limiting glial membrane and the advanced alterations in the parenchymatous structures with the dissolution of the ganglion cells. No less significant is selective involvement of the motor areas in the cortex. In rabies encephalitis are the Negri bodies and, perhaps, the greater glial activity, to which may be added, as observed by Spatz, polymorphonuclear leukocytic infiltrations in the acute stage. Aside from this geographic and moderate cytologic distinction there is no way of identifying the separate members of this group, unless clinical factors are drawn on and the deep imprints left in the wake of the slowly or rapidly advancing process on the restricted and anatomically distinct areas of the central nervous system can be read clearly and with certainty. Such is the case when one considers the selective loss of neurons in the motor areas of the brain and cord in the Heine-Medin form of encephalomyelitis, or the limitations of such anatomic alteration to the substantia nigra in acute epidemic encephalitis.

5. *Acute Disseminated Demyelinizing Encephalomyelitis.*—This group has during recent years forged its way to the foreground, as clinical observations have accumulated and anatomic studies have multi-

34. Spatz, H., and Seifried, O.: Die Ausbreitung der enzephalitischen Reaktion bei der Bornaschen Krankheit der Pferde und deren Beziehungen zur Encephalitis epidemica, zur Heine-Medinschen Krankheit und zur Lyssa des Menschen, Ztschr. f. d. ges. Neurol. u. Psychiat. **124**:317, 1930.

plied (Redlich,[35] Pette,[36] Demme,[37] Spiller,[38] Guillain and others[39]). It has gained a prominent place in clinical neurology and has stimulated intensive work in neuropathology. Because it resembles clinically and anatomically the so-called acute multiple sclerosis, it is believed to hold a key position with relation to the problem of multiple sclerosis. Many who applied themselves to a study of this disease form were inspired by the hope of obtaining a clearer understanding of its pathogenesis, which in turn would aid materially in the recognition of the causative factors operating in the classic form of multiple sclerosis.

Indeed, it is granted by all observers that there is a great similarity between the two conditions, that is, between acute encephalomyelitis and multiple sclerosis, and as this feature will be discussed by others I shall, to obviate needless repetition, proceed with a discussion of the morphologic features. It is also common knowledge that in the gross appearance and the general distribution of the lesion there is a great similarity between the two maladies. But beyond this there is a decided division of opinion. There are those who claim that in acute disseminated encephalomyelitis the disease is distinctly inflammatory, though associated with a demyelinizing process, while in multiple sclerosis they see an essentially degenerative condition. They are aware of an occasional inflammatory reaction in multiple sclerosis, but regard it as symptomatic and secondary. Then there are those who consider both diseases inflammatory and regard the anatomically ripe instances of multiple sclerosis as the end-result of the inflammatory process noted in acute multiple sclerosis or its homolog, acute disseminated encephalomyelitis. They interpret the remissions and exacerbations, a diagnostic

35. Redlich, E.: Ueber ein gehäuftes Auftreten von Krankheitsfällen mit den Erscheinungen einer Enzephalomyelitis disseminata, Monatschr. f. Psychiat. u. Neurol. **64**:152, 1927.

36. Pette, H.: Zur Frage der infektiösen Aetiologie der akuten disseminierten Enzephalomyelitis respektive der akuten multiplen Sklerose, München. med. Wchnschr. **74**:1409, 1927.

37. Demme, Hans: Ein Beitrag zur Frage der „akuten multiplen Sklerose," Deutsche Ztschr. f. Nervenh. **117-119**:81, 1931.

38. Spiller, W. G.: Encephalomyelitis Disseminata, Arch. Neurol. & Psychiat. **22**:647 (Oct.) 1929.

39. Guillain, G., and Garcin, R.: Le syndrome paralytique unilatéral global des nerfs craniens, Ann. de méd. **24**:76, 1928. Foix, C., and Alajouanine, T.: La myélite nécrotique subaiguë, Rev. neurol. **2**:1, 1926. Anton, G., and Wohlwill, F. R.: Multiple nicht-eitrige Enzephalomyelitis und multiple Sklerose, Ztschr. f. d. ges. Neurol. u. Psychiat. **12**:31, 1912. Martin, J. P.: Acute Disseminated Encephalo-Myelitis, Lancet **2**:628, 1928. Grinker, R. R., and Bassoe, Peter: Disseminated Encephalomyelitis: Its Relation to Other Infections of the Nervous System, Arch. Neurol. & Psychiat. **25**:723 (April) 1931. Ley, R. A., and van Bogaert, Ludo: Sur les formes basses de l'encéphalite epidémique, J. de neurol. et de psychiat. **28**:19, 1928.

feature in the typical forms of multiple sclerosis, as relighting and fading out incidents in a latent inflammatory disease.

The gap between these two extreme views is still wide open, and there is little hope that it will be bridged over very soon, unless the inciting agent in one or both disease forms is discovered. Up to the present time the intensive studies of this disease have been rewarded mainly by a number of well established morphologic data, which may aid in the search for the excitant but have left it as yet unrecognized.

The accounts of the morbid anatomy in acute demyelinizing disseminated encephalomyelitis usually begin with a description of the numerous patches of demyelinization, which are at times discrete and at other times less sharply outlined and confluent with other similar patches. This is the most patent anatomic feature and is, perhaps, too readily accepted as the essential morphologic character of the disease. As in the case of the adventitial infiltrations, it is necessary here also to guard against erroneous deduction, for demyelinization, a term that delegates to the excitant an inherent pathogenic potency, occurs also in conditions in which the etiologic factors do not admit of the specificity of the demyelinizing agent. This is well illustrated by two disease entities of divergent origin, as in Binswanger's disease, the so-called chronic subcortical encephalitis (Farnell and Globus [40]) and dementia paralytica (Spielmeyer). In expressing this view with regard to the demyelinizing potencies of some noxious agents, it is realized that the recent work on the pathogenesis of multiple sclerosis by Weil,[41] Brickner [42] and Putnam [43] and the still more fundamental contribution to the study of the specific character of organ lipoids by Moran [44] make it highly advisable to remain for the present in a position of strict neutrality.

These so-called areas of demyelinization are recognized in myelin preparations as bald spots (figs. 8 and 9). They have no regularity in distribution, occurring alike in gray and white substance, with some preference for the white substance. Often one or more of such lesions may involve contiguous areas of white and gray substance. But in spite of the lack of definite areas of predilection there are two constant seats of the lesions: the chiasm and the optic tracts and nerves and

40. Farnell, F. J., and Globus, J. H.: Chronic Progressive Vascular Subcortical Encephalopathy, Arch. Neurol. & Psychiat. **27**:593 (March) 1932.

41. Weil, Arthur: A Study of the Etiology of Multiple Sclerosis, J. A. M. A. **97**:1587 (Nov. 28) 1931.

42. Brickner, R. M.: Studies on the Pathogenesis of Multiple Sclerosis, Arch. Neurol. & Psychiat. **23**:715 (April) 1930.

43. Putnam, J. T.: Acute Multiple Sclerosis in Dogs, Arch. Neurol. & Psychiat. **24**:640 (Sept.) 1930.

44. Moran, F.: Zur Entstehung von Lipoidantikörpern nach Vorbehandlung mit Organsuspensionen, Ztschr. f. Immunitätsforsch. u. exper. Therap. **67**:115, 1930.

the subependymal zone adjacent to the walls of the lateral ventricles. This, however, is to be accepted for the time being on its face value alone, as some uncertainty is reflected by the fact that these two zones are not regularly examined in other diffusely disseminated diseases of the central nervous system. It is not inconceivable that had such examinations been made lesions varying in intensity would have been disclosed, and this would minimize the significance of this geographic landmark in acute encephalomyelitis. Under the microscope the disease areas reveal fully developed features of inflammatory reaction,

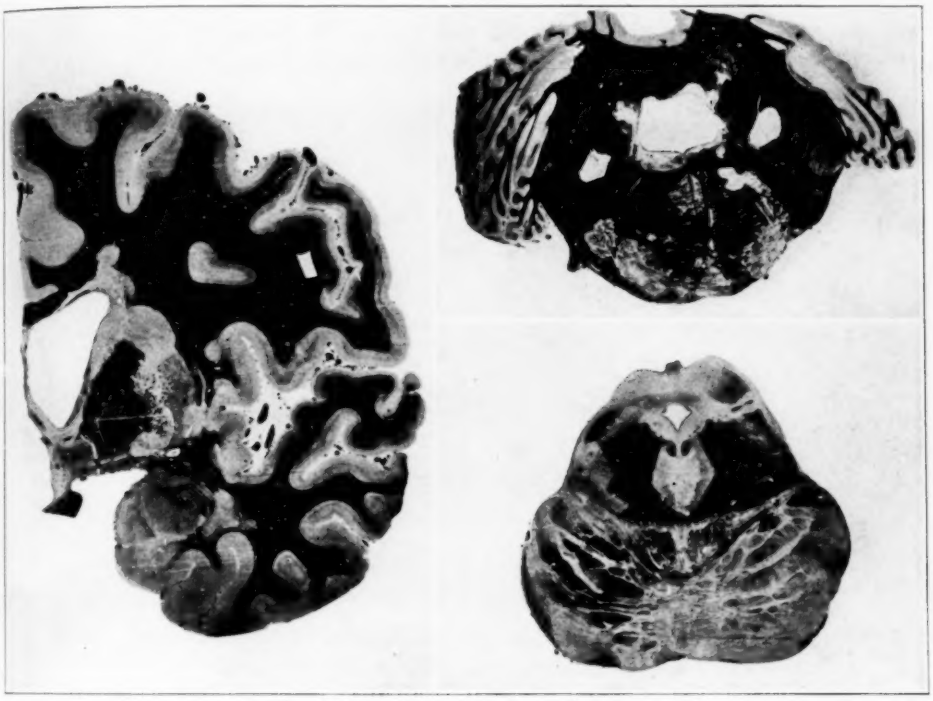

Fig. 8.—Distribution of areas of demyelinization in acute disseminated sclerosis (disseminated encephalomyelitis).

such as lymphocytic infiltrations in the adventitial spaces, proliferation of the several varieties of neuroglia and dissolution of myelin with loss of axis cylinders, in a degree that is said to be at variance with the loss of myelin. There is, of course, a wide range of variations in the cellular character of a given lesion paralleling the acuity of chronicity of a given disease focus. Highly significant, however, is the fact that the mesodermal reaction is a constant finding. The intensity and the constancy of the mesodermal reaction point to an inflammatory and hence infectious character of the process. One who questions the true inflammatory nature of this condition and is inclined to regard the mesodermal

response as a reactive phenomenon provoked by the dissolution of myelin and the subsequent liberation of foreign products need but be reminded of the massive dissolution of myelin in the several systemic diseases of the spinal cord, where mesodermal reactions are entirely absent or are only highly restricted in extent and intensity.

The gliogenous elements participate prominently and extensively in the development of the lesions. In the earlier stages the microglia type plays an active rôle, but as the focal disease process matures the microglia is replaced by proliferating macroglia.

The third constant alteration is the demyelinization and the loss of axis cylinders. It is claimed, particularly by those who see in this disease a form allied to multiple sclerosis, that the destruction of

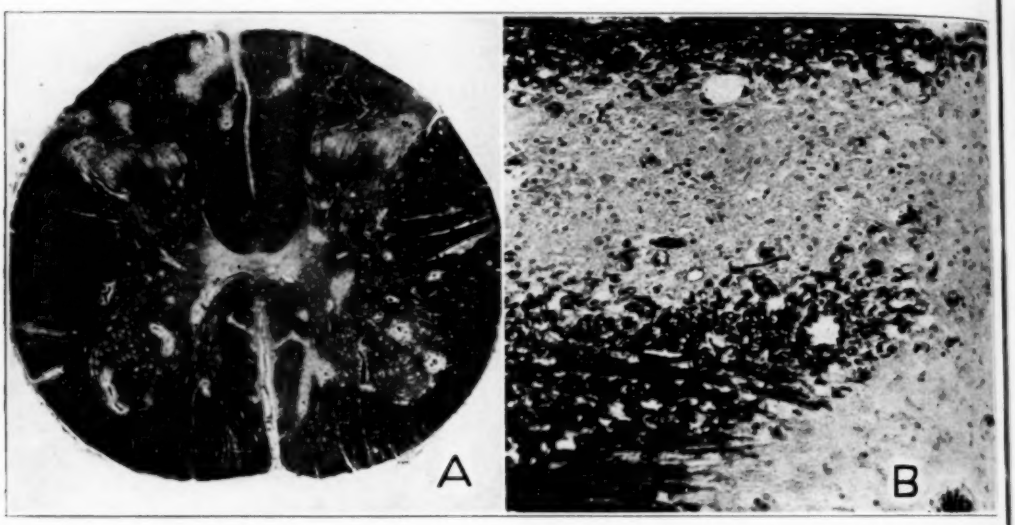

Fig. 9.—*A*, less discrete areas of demyelinization in a section of the spinal cord in acute disseminated encephalomyelitis. *B*, area of demyelinization under high power. Spielmeyer myelin stain.

axis cylinders does not follow in degree the process of demyelinization, but the observations are based on rather crude methods of estimation and should not be accepted without more careful studies.

There is a great temptation to ally acute disseminated encephalomyelitis with so-called acute multiple sclerosis (Marburg[45]) and to regard both disease forms as the forerunners of the classic multiple sclerosis (Pette[46]), particularly since in the latter are often found

45. Marburg, O.: Die sogenannte akute multiple Sklerose (Encephalomyelitis periaxialis scleroticans), Jahrb. f. Psychiat. **27**:211, 1906.

46. Pette, H.: Klinische und anatomische Studien: Ueber die Pathogenese der multiplen Sklerose, Deutsche Ztschr. f. Nervenh. **105**:76, 1928.

old, fully matured plaques alongside of fresh, more or less diffuse foci which are strikingly similar in structure to those seen in acute multiple sclerosis and acute encephalomyelitis. Not unreasonable are the claims that acute encephalomyelitis is not a new disease, but is only a new name for what was previously regarded as acute multiple sclerosis. Not without ground is the belief that the failure to take into account the probable fate of cases of acute disseminated encephalomyelitis, in which death, interrupting a further sequence of events, obstructed a clearer view of the relationship of acute disseminated encephalomyelitis and multiple sclerosis.

Pette, among others, has made out a good case for the position he takes in regard to encephalomyelitis and acute multiple sclerosis as conditions identical in morphology and etiology. There is little doubt now that both are infectious in origin. With the assumption that these conditions reduplicate many, if not all, of the features of multiple sclerosis, it would be inferred that the latter disease is also inflammatory in nature. This, however, cannot and need not as yet be accepted or rejected without additional proof.

6. *Perivenous Encephalomyelitis.*—This form of disseminated encephalomyelitis has many anatomic features in common with the preceding type of inflammatory disease of the cerebrospinal axis, and could be grouped with the latter were it not for some minor anatomic differences and that in the perivenous type there is always a known antecedent systemic infection.

The best known example of this form is the so-called postvaccinal encephalomyelitis, an acute and severe inflammatory disease of the brain and cord, which is precipitated by immunization against smallpox. Grouped about the postvaccinal encephalomyelitis are several anatomically similar postinfectious encephalitides, which develop in the course of an exanthematous disease, such as measles, chickenpox and smallpox.

The alarming increase in the frequency with which manifestations of this grave disease follow vaccination has attracted the attention of many competent observers.[47] As a result there now are reliable accounts

47. Lucksch, Franz: Gibt es beim Menschen eine Vakzine-Encephalitis? Centralbl. f. Bakt. **96**:309, 1925. Van Bastiaanse, B.: Die in Holland beobachteten Fälle von Enzephalomyelitis postvaccinalis bis zum Januari, 1929, Ztschr. f. d. ges. Neurol. u. Psychiat. **134**:657, 1931. Turnbull, M. H., and McIntosh, James: Encephalo-Myelitis Following Vaccination, Brit. J. Exper. Path. **7**:181, 1926. Bouman, L., and Bok, S. T.: Die Histopathologie der Encephalitis post vaccinationem, Ztschr. f. d. ges. Neurol. u. Psychiat. **111**:495, 1927. Pedran, J. R.: The Histology of Postvaccinal Encephalitis, J. Path. & Bact. **31**:17, 1928. Turnbull, H. M.: Encephalo-Myelitis in Virus Diseases and Exanthemata: Histology of Post-Vaccinal Encephalitis, Brit. M. J. **2**:331 (Aug. 25) 1928. Hassin, G. B., and Geiger, J. C.: Postvaccinal (Cowpox) Encephalitis, Arch. Neurol. & Psychiat. **23**:481 (March) 1930.

of the clinical features and anatomic alterations in the disease. But unfortunately the interpretations of these observations are somewhat varied and less satisfactory. This is seen in the attempts to assemble the postvaccinal encephalitides into a clinically homogeneous group,

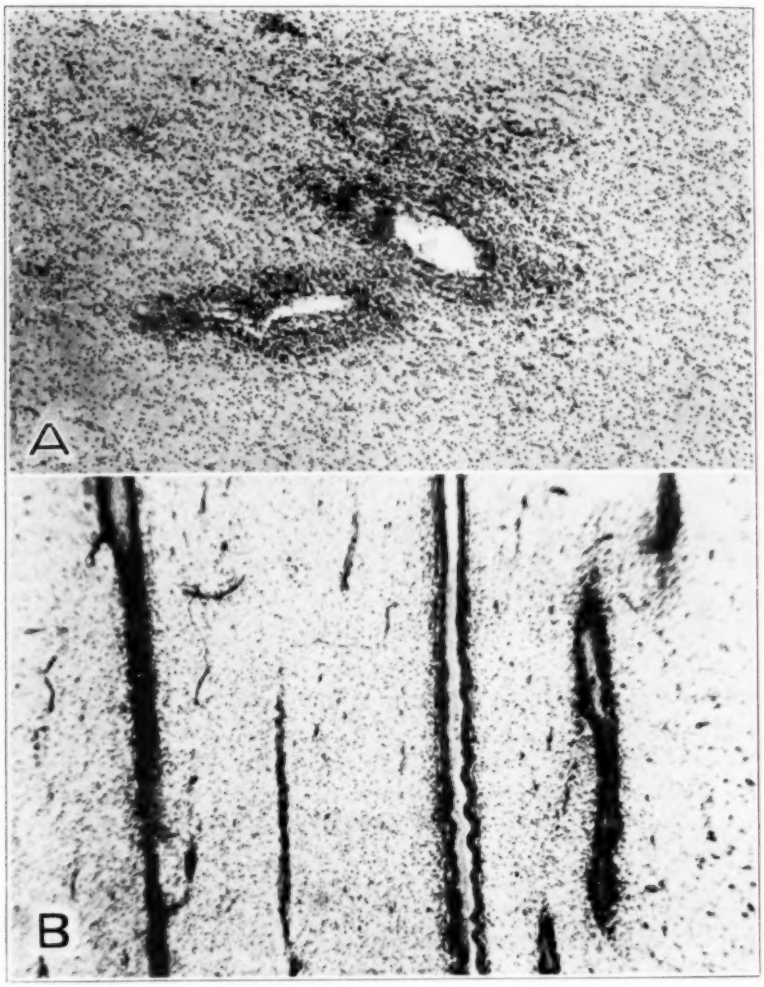

Fig. 10.—*A*, perivenous infiltrations in postvaccinal encephalomyelitis. *B*, seam-like perivenous infiltration in postvaccinal encephalomyelitis. Nissl stain.

such general symptoms as headache, vomiting, clouded intellect, drowsiness, pyrexia, disturbances of the ocular muscles and occasional convulsions being used as distinctive clinical features. It is obvious that such manifestations are in keeping with the anatomic changes and point merely to the severity and the wide distribution of the disease.

The latter finds further support in the great diversity in the symptomatology in the reported cases. Some of the cases were typified by outspoken meningeal signs, some by convulsive seizures, some by palsies of the cranial nerves, some by predominance of signs referable to the brain and some by signs pointing to disease of the spinal cord. Thus, it would seem that clincally, aside from its severity as shown by the grave clinical picture and the high mortality, the disease process behaves

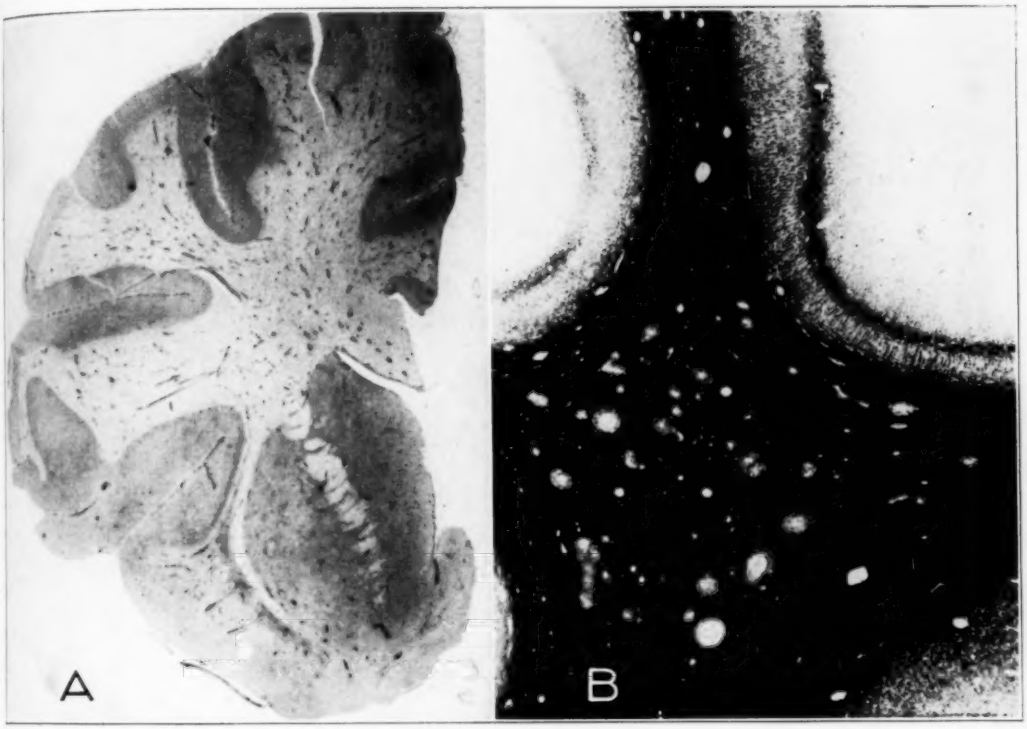

Fig. 11.—*A*, the wide distribution of the perivenous infiltrations, more discrete in the white substance, but also seen in the gray substance (postvaccinal encephalomyelitis). Nissl stain. *B*, areas of demyelinization as seen in a Spielmeyer-stained preparation (postvaccinal encephalomyelitis).

not unlike any other diffuse or disseminated inflammatory disease of the central nervous system.

As the name perivenous encephalomyelitis implies, the main distinguishing feature of this form is in the predilection of the inflammatory changes for the smaller and medium-sized veins (fig. 10 *A*), often assuming a seamlike arrangement about the vessels (fig. 10 *B*). The lesions are widely distributed (fig. 11 *A*) and are less sharply demarcated than in acute multiple sclerosis. They show no preference for the white

or gray matter. They are perhaps more discernible in the white matter, but are just as frequent in the gray matter. The demyelinizing character of the process is stressed by all who described this disease

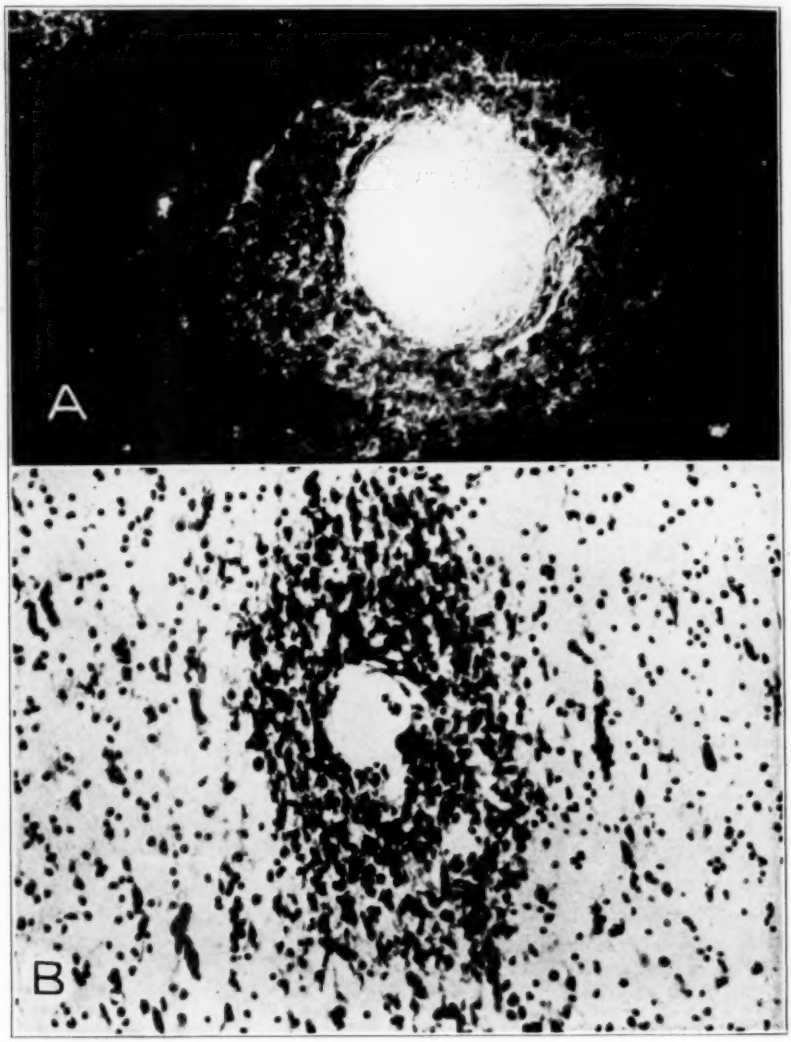

Fig. 12.—*A*, one of the so-called areas of demyelinization (seen in fig. 11 *B*) under higher magnification (postvaccinal encephalomyelitis). *B*, so-called glial mobilization about a vessel in postvaccinal encephalomyelitis. Nissl stain.

(fig. 11 *B*). As will be noted in figure 12 *A*, however, it is obvious that if areas of apparent demyelinization are scrutinized carefully with a higher magnification and special staining methods are used it will be

found that the adventitial spaces are distended with cellular infiltrations (fig. 12), displacing myelinated fibers so as to create light areas about blood vessels. These areas may erroneously be assumed to be zones of demyelinization.

It is also said that the glial reaction is here more prominent than the mesodermal. This is the first impression one receives on a rapid survey of the material (fig. 12*B*), but a more careful study will disclose pronounced and clearly discernible lymphocytic infiltrations (fig. 13*A*), and many of the cells that are regarded as glial will be found to be of lymphocytic character.

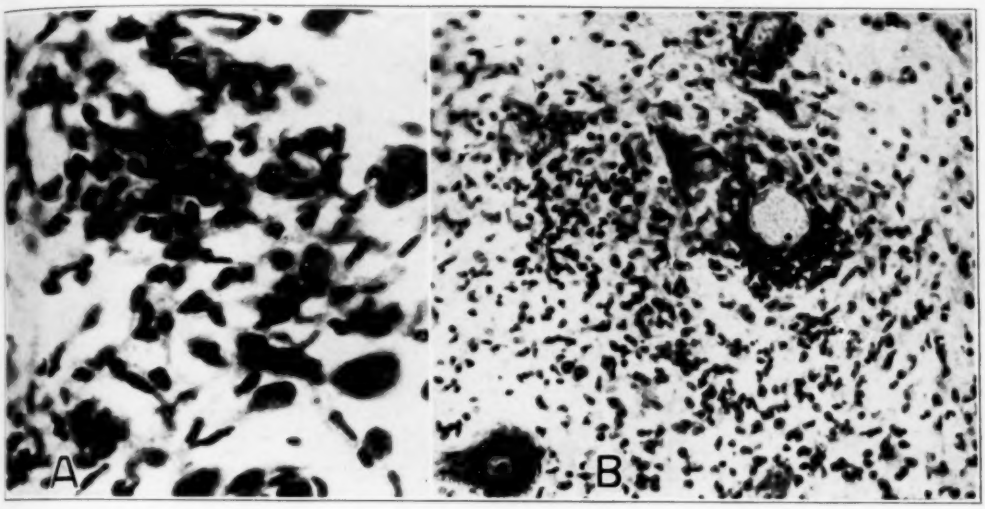

Fig. 13.—*A*, microglial (?) nodule under higher magnification in postvaccinal encephalomyelitis. *B*, central lymphocytic infiltration with peripheral zone of glial proliferation; postvaccinal encephalomyelitis. Nissl stain.

It is rather too readily assumed that a cell, when it is somewhat oblongated and irregular in outline and has blunt processes, is a microglia. When it fails to stain with silver, it is claimed that the methods are inadequate, and the cell is still considered microglia. I believe that greater care must be exercised in grouping the cells, if one is to base interpretations of the disease on the character of cellular reactions. It is not conceivable that some of these cells are lymphocytes that have acquired migrating forms. Recently, in the study of migrating lymphocytes, such forms have been demonstrated.[48] It is not improbable that

48. Katzenstein, Ruth: Untersuchungen über die Umwandlungsfähigkeit der Lymphzellen, Virchows Arch. f. path. Anat. **281**:172, 1931.

because of this difficulty Spielmeyer introduced the term polyblastic glia to denote a similarity between the morphologic potencies of Maximow's polyblasts and those of the undifferentiated migrated gliogenous structures, which as yet cannot be identified with any of the mature forms of glia.

To return to the histologic character of the lesions, one finds in the infiltrations lymphocytes, plasma cells, mononuclear leukocytes,

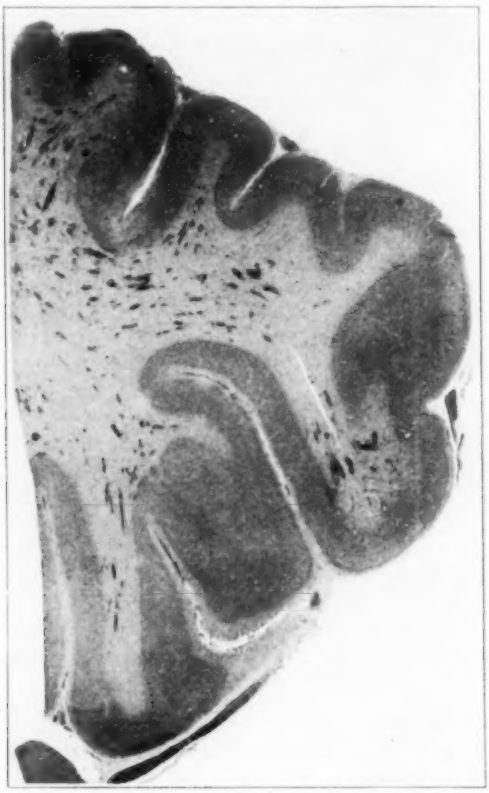

Fig. 14.—Perivenous lesions in measles encephalomyelitis (compare with fig. 11 *A*).

some histiocytes or polyblasts and glia cells. Among the latter are many compound granular cells.

Highly significant is the frequent finding of vessels that show a central ring of lymphocytic infiltration surrounded by a peripheral radiating zone of glial aggregation (fig. 13 *B*). This feature, when added to the fact that, aside from the more pronounced gliosis, greater

disruption of the limiting glial membrane, wider extravascular invasion by lymphocytic and glial elements and the so-called process of demyelinization, there are no deviations from the characteristic anatomic picture

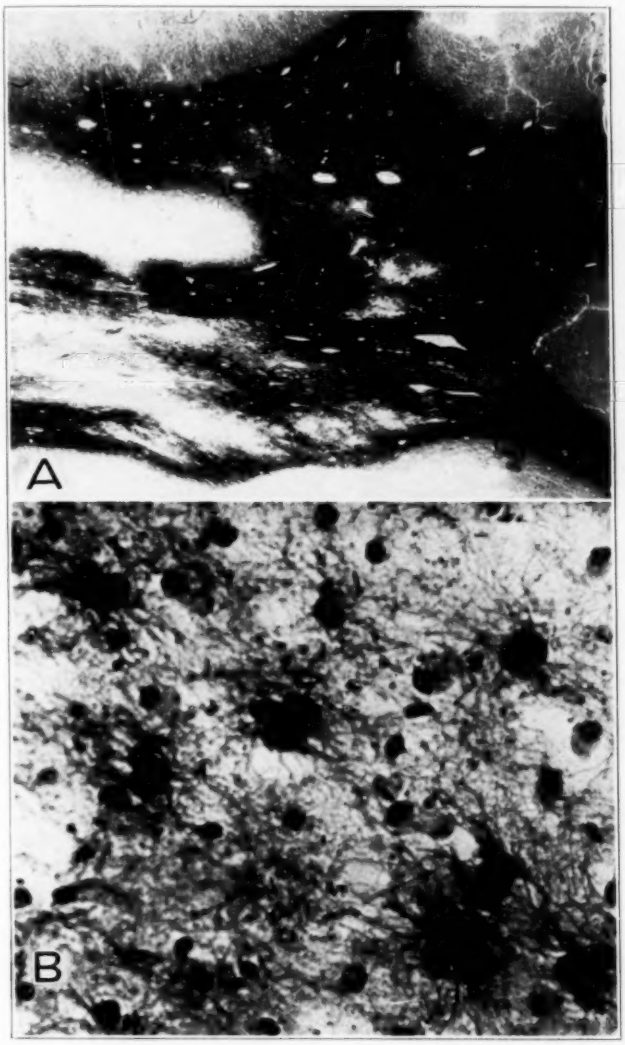

Fig. 15.—*A*, confluency of the demyelinized areas in an older case of measles encephalomyelitis. Spielmeyer myelin stain. *B*, gliosis in an older case of measles encephalomyelitis. Hortega stain.

of essential encephalitis, leads one to conclude that the postinfectious forms of encephalomyelitis differ only in degree from other forms of inflammatory disease in the central nervous system.

In measles encephalitis one finds a similar anatomic picture[49] (fig. 14). This applies to material obtained in the initial stage of the disease. The selection of zones at the margin of the cord and, less often, at the marginal zones of the cerebral cortex and the subependymal layer is considered a characteristic of this form.[50] In the more advanced stages the anatomic picture changes. The demyelinized areas are more extensive and diffuse (fig. 15 *A*). The mesodermal reaction disappears rapidly, and instead the glial reaction dominates the scene (fig. 15 *B*). The large number of compound granular cells and the various transitional forms of glia, diffusely spread over the white matter, give it an

Fig. 16.—The apparent limitation of the lesion to the subcortex, as shown by the greater amount of liberated fat in the subcortex. Herxheimer scharlach R stain.

appearance not unlike that seen in the degenerative lesions, as in acute forms of diffuse gliosis (fig. 16.) This is significant in the interpretation of lesions described under the name of Schilder's disease.

In chickenpox encephalitis the histologic alterations are similar to those in postvaccinal and measles encephalitis (fig. 17). Through

49. Greenfield, J.: The Pathology of Measles Encephalomyelitis, Brain **52**: 171, 1929. Ferraro, Armando, and Scheffer, I. H.: Encephalitis and Encephalomyelitis in Measles: A Pathologic Report of Six Cases, Arch. Neurol. & Psychiat. **25**:748 (April) 1931.

50. Wohlwill, F.: Ueber Encephalomyelitis bei Masern, Ztschr. f. d. ges. Neurol. u. Psychiat. **112**:20, 1928.

Professor Spielmeyer, I was able to familiarize myself with the anatomic alterations in this type of postinfectious encephalitis. A full description of his material is given by van Bogaert and is referred to in a recent discussion by Spielmeyer.[51] The latter emphasized the wide distinction of axis cylinders, proportionate to the loss of myelin, as a feature distinguishing the disease of the brain from multiple sclerosis.

It is now common practice, when discussing the pathogenesis of the so-called demyelinizing encephalitis, to include Schilder's disease, a disease form that in a typical case is characterized by its discrete limitation to the white substance of the cerebral hemispheres, glial proliferation, demyelinization and less constant lymphocytic infiltration. Here

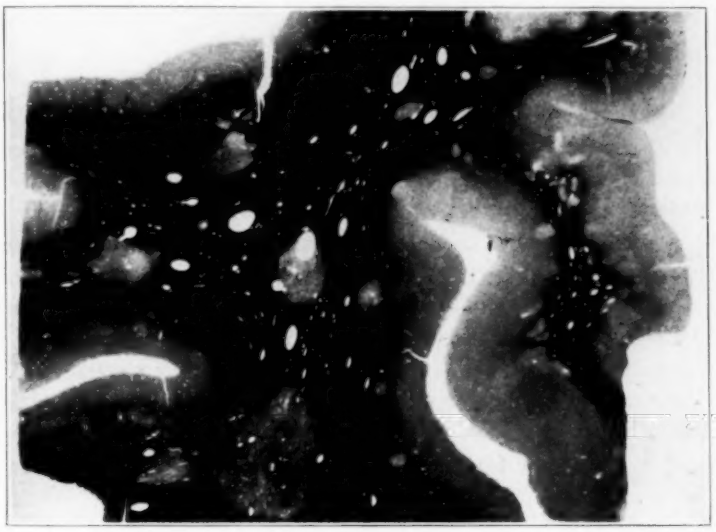

Fig. 17.—Disseminated areas of demyelinization in chickenpox encephalomyelitis. Spielmeyer myelin stain.

also there are two camps; in one are those who believe it to be a form of degenerative encephalopathy. In the other are those who hold firmly to the conviction that it is of inflammatory character, hence the name encephalitis periaxialis diffusa. Both groups have what they consider valid observations to support their views. I believe that facts do not yet warrant a consideration of this diffuse process as a type of encephalomyelitis, though, as Globus and Strauss [52] and Spielmeyer [23] have said,

51. Spielmeyer, W.: Vergleichend anatomische Betrachtungen über einige Encephalitiden, insbesondere über den Typus der Impfencephalitis, Ztschr. f. Hyg. u. Infektionskr. **113**:170, 1931.

52. Globus, J. H., and Strauss, Israel: Progressive Degenerative Subcortical Encephalopathy, Arch. Neurol. & Psychiat. **20**:1190 (Dec.) 1928.

some of the instances recorded may rightfully be grouped with them. At present it is safer not to take too definite a position, but to await further studies on its pathogenesis. It is not unlikely that the same error is being repeated that occurred when every diffuse subcortical lesion in which glial proliferation was dominant was named diffuse sclerosis, and every diffuse demyelinizing and gliosing disease of the cerebral hemispheres of unknown etiology was considered Schilder's disease. Is it not possible that these are end-results of a great variety of disease processes terminating in demyelinization and gliosis? If this is true, then it may be said that some of them have an encephalitic process as their forerunner. Certainly it is too early to speak with great freedom of the noxious agent until a decision has been reached as to the pathogenesis of this puzzling condition.

SUMMARY

In the foregoing pages I have attempted to define some of the issues that are essential to a clear delimitation of the problems concerning inflammatory diseases of the central nervous system. With the aid of the views held by competent investigators and supported by my own observations, I have narrowed the concept of encephalitis and encephalomyelitis to include only conditions in the central nervous system in which an infectious agent may be postulated with a reasonable degree of certainty and may be accepted as the essential etiologic factor.

In logical sequence the problem of classifying encephalitides had to be dealt with, and conservative views, based on more or less firmly established facts, have been followed. Thus, grouping on the grounds of minor histologic differences or on the basis of biologic discriminations of still doubtful character has been avoided, and a tentative classification, to meet practical needs, has been introduced with more constant histologic and topographic variations as a guide.

It has been emphasized that in any attempt to widen this classification, one must guard against giving recognition to plausible but yet doubtful biologic theories.

By placing side by side the various forms of inflammatory disease of the central nervous system, a striking confluency of all the encephalitic forms has been revealed, and it has been suggested that the minor histologic differences express mainly the degree rather than the character of the pathologic process, and it is not unlikely that there are variations in intensity of the excitant and variations in the local vulnerability of the tissue rather than with distinct types of causative agents.

In conclusion it may be said that the anatomist is not in a favorable position to bring the problem to a final solution. Purely anatomic methods now, as in the past, are inadequate to discover the causative

agent. It is the experimental biologist, led by the resourceful and tenacious workers in this field of research,[53] who will have the sole opportunity and the good fortune to attain this goal. The anatomist, by strict adherence to facts observed and by guarding against hasty and erroneous interpretations, will continue to serve the experimental biologist in providing him with useful information.

53. Editorial: Allergic Reaction in Poliomyelitis, J. A. M. A. **97**:1006 (Oct. 3) 1931; Experimental Poliomyelitis, ibid. **97**:1711 (Dec. 5) 1931.

THE BRAIN IN ACUTE RHEUMATIC FEVER

NONSUPPURATIVE MENINGO-ENCEPHALITIS RHEUMATICA

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Acute rheumatic fever is a general infection. Its major manifestations are fever, drenching sweats and polyarthritis. The heart may be and usually is involved. One attack does not confer immunity, but on the contrary makes a person more susceptible to recurrences. It must always be kept in mind that one or more of the symptoms may so overshadow the others that there is danger of overlooking the basic condition. It is not rare to find a patient with a typical rheumatic heart disease without a clue to a former rheumatic infection.

All the organs of the body may be involved in the general infection, and all may show inflammatory and degenerative reactions (Swift [1] and Veil [2]). The organ that is notoriously involved is the heart (Fahr [3]), but the kidneys (Stettner [4]), lungs (Rabinowitz,[5] Paul [6] and Naish [7]) and other internal organs (Holsti [8]) and the vascular system (von

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From the Wards and Laboratories of the Philadelphia General Hospital, Temple University Medical School, and the Graduate School, University of Pennsylvania.

1. Swift, H. F.: Rheumatic Fever, J. A. M. A. **92**:2071 (June 22) 1929.

2. Veil, W. H.: Die „rheumatische Infektion," Deutsche med. Wchnschr. **54**: 1539, 1928.

3. Fahr, T.: Beiträge zur Frage des Herz und Gelenkveränderungen bei Gelenkrheumatismus und Scharlach, Virchows Arch. f. path. Anat. **232**:134, 1921.

4. Stettner, Erlangen: Ueber Polyarthritis acuta im Kindesalter, Deutsche med. Wchnschr. **55**:261, 1929.

5. Rabinowitz, M. A.: Rheumatic Pneumonia, J. A. M. A. **87**:142 (July 17) 1926.

6. Paul, J. R.: Pleural and Pulmonary Lesions in Rheumatic Fever, Medicine **7**:383 (Dec.) 1928.

7. Naish, A. E.: The Rheumatic Lung, Lancet **2**:10 (July 7) 1928.

8. Holsti, O.: Beitrag zur Kenntnis des Magen-Nephro und Kardio-pathien, Arb. a. d. path. Inst. zu Helsingfors **4**:415, 1926.

Glahn and Pappenheimer [9] and Sachs [10]) do not escape its ravages. Among the internal organs that may be affected is the brain. It is rather unusual that the same infection which in the adult produces polyarthritis may, in the child, cause acute chorea. It is true that acute rheumatic fever occurs in childhood, but it is also true that the acute chorea of Sydenham is extremely rare in adult life and preponderates during childhood (Lewy [11]). Pregnancy appears to bring out in many instances an acute chorea that had been present during childhood. The close relationship between acute chorea and acute rheumatic fever is shown by the fact that in both, the same type of endocardial damage may result (Poynton and Holmes,[12] Greenfield and Wolfsohn,[13] Lhermitte and Pagniez [14] and Castrén [15]).

As a rule, the clinician does not consider the manifestations of the brain as an important part of the picture of acute rheumatic fever. More and more is it being learned that the brain is as much a part of the body as are the heart and kidneys. In the course of general infections and toxemias it is practically impossible for the brain to escape some damage, either temporary or permanent. It is true that, as a rule, the cerebral symptoms are transient, but occasionally permanent manifestations may remain (Williams,[16] Coombs [17] and Hoppe [18]). While these permanent manifestations are usually dependent on an endocardial condition, it is possible to have such severe changes in the brain at the time of the original infection that mental and physical invalidism can remain, yet it is absolutely true that even in cases with intense chorea the patient may recover completely; this shows that the changes in the brain are transient. In the older literature one reads of "cerebral rheumatism." The mental symptoms occurring in the course of acute rheumatic fever are considered as cerebral rheumatism no

9. von Glahn, W. C., and Pappenheimer, A. M.: Specific Lesions of Peripheral Blood Vessels in Rheumatism, Am. J. Path. **2**:235, 1926.

10. Sachs, Benjamin: The Pathology of Rheumatic Fever: A Critical Review, Am. Heart J. **1**:730, 1925-1926.

11. Lewy, F. H.: Die Histopathologie der choreatischen Erkrankungen, Ztschr. f. d. ges. Neurol. u. Psychiat. **35**:622, 1923.

12. Poynton, F. J., and Holmes, G. M.: Chorea and Vessel Changes, Lancet **2**:982, 1906.

13. Greenfield, J. G., and Wolfsohn, J. M.: The Pathology of Sydenham's Chorea, Lancet **2**:603 (Sept. 16) 1922.

14. Lhermitte, J., and Pagniez, P.: Pathological Anatomy and Physiology of Sydenham's Chorea, Encéphale **25**:24, 1930; Cerebral Lesions in Acute Chorea, Arch. de méd. d. enf. **33**:156, 1930.

15. Castrén, H.: Zur pathologische Anatomie der akuten Chorea (Sydenhamschen), Arb. a. d. path. Inst. zu Helsingfors **3**:371, 1925.

16. Williams, E. M.: Cerebral Rheumatism, New York M. J. **94**:478, 1911.

17. Coombs, C.: Cerebral Rheumatism, Practitioner **88**:99, 1912.

18. Hoppe, H.: Cerebral Rheumatism, Lancet-Clinic **105**:219, 1909.

matter how mild or severe they may be. The older authors, and in particular the French school led by Trousseau,[19] saw in the symptoms of the brain a manifestation of a toxic involvement of the structure of the brain which they attributed to the hyperpyrexia. The symptoms, as ordinarily seen, vary from restlessness, nervousness and delirium, which may be of a muttering type, to a more severe mental course such as depression or hyperactivity, or may even lead to an actual psychosis. With the infection and toxemia overwhelming the patient, convulsions and coma occur, terminating in death. Choreic manifestations or meningeal involvement may dominate the cerebral picture. As regards the pathology, little can be found in recent literature on the brain in acute rheumatic fever. The literature can be divided into three periods: 1. The pre-Nissl period, in which were described only gross lesions in the meninges and brain, depending largely on the results of embolic phenomena (Sydenham[20] and Rosenthal and Joffe[21]). 2. The period of Nissl when, as the result of finer staining methods, changes in the ganglion cells in the form of neuronophagia and chromatolysis, an increase in fat around the blood vessels, a moderate meningeal thickening and overgrowth of glia cells and occasional mild perivascular infiltration were described. 3. In the third or modern period, not only are there available the silver stains of Cajal and Hortega, but an increasing knowledge of the mechanics within the cranium has been of value in the elucidation of this important problem. In view of the light that more modern methods have thrown on the pathology of the brain in general, it was thought that a histologic study of five cases might be of value.

REPORT OF CASES

CASE 1.—*Polyarthritis, fever and sweats for seven weeks, with a soft systolic apical murmur. Later, lethargy, delirium and purpuric spots on the skin, which continued to death. At autopsy, no valvular vegetations; principal changes in the brain: productive endarteritis of the small cortical and subcortical vessels, chromatolysis of the cells, occasional "Verödungsherde" and marked edema.*

History.—J. D., a white man, aged 32, who was admitted to the Philadelphia General Hospital, to the service of Dr. Schnabel, on Aug. 4, 1926, had become ill five weeks previously, with cough and pain in the chest. Shortly after the onset, pain, redness and swelling developed in the left knee, later in the right knee and then in the right index finger. There was a family history of rheumatic fever and of chorea.

Examination.—At the time of admission, the case was typical of acute rheumatic fever, associated with a mild rise of temperature to 100 F. The heart was enlarged, and there were a soft systolic murmur at the apex and a presystolic thrill. The pulse rate averaged 120 per minute. Swelling and tenderness continued to involve joint after joint. The tonsils were small and embedded.

19. Trousseau, A.: Clin. méd. de Hôtel Dieu **2**:22, 1856.

20. Sydenham, T., cited by Girard: Thèse de Paris, 1862.

21. Rosenthal and Joffe: Bull. et mém. Soc. méd. d. hôp. de Paris **25**:683, 1908.

Course.—The patient was kept in bed, and the ordinary remedies were applied. On August 10, there was apparent improvement, but the lethargy was out of proportion to the clinical picture. The pulse rate had decreased under moderate doses of digitalis. Delirium was observed on this date for the first time. On August 14, the patient went into collapse. The temperature at this time was 104 F.; the pulse rate was 120. On the following day, the condition appeared slightly improved,

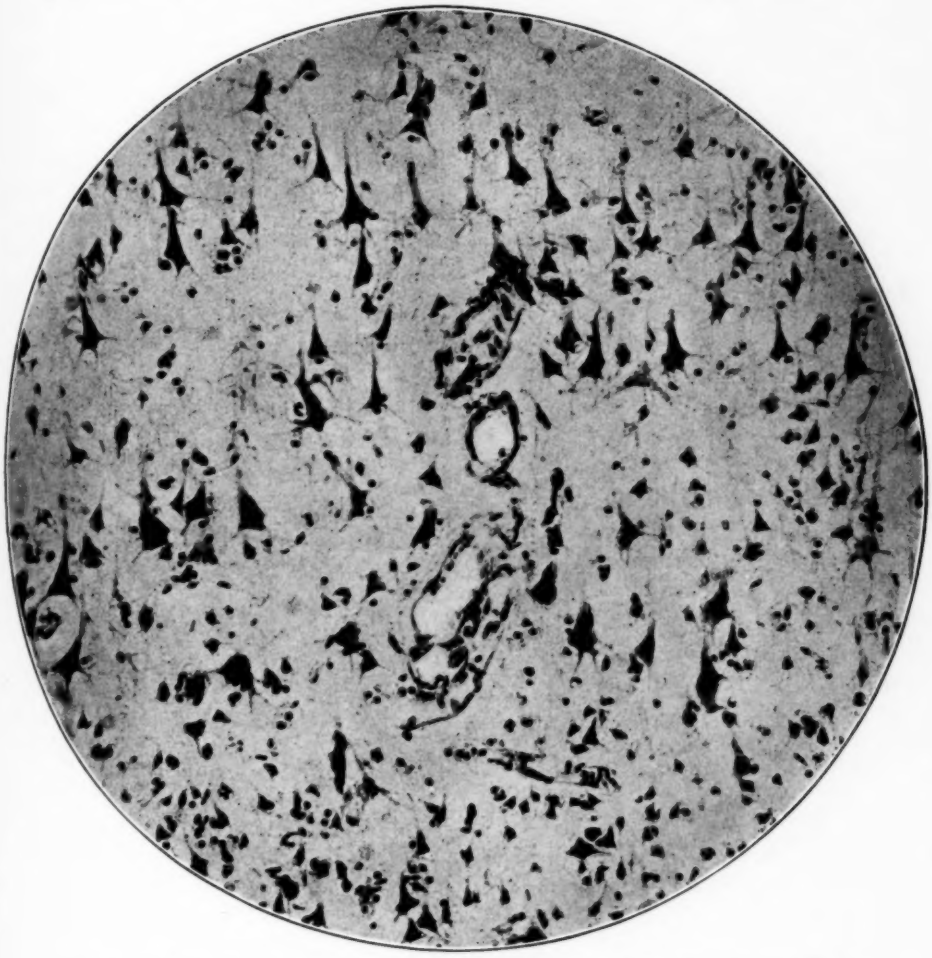

Fig. 1 (case 1).—Gefässpaket. The tortuous vessel in the cortex was cut at different angles. The swollen endothelial cells can be easily made out.

but he was weak and at times irrational. On August 17, purpuric spots were noticed on various parts of the body. On August 18, the patient was very lethargic and showed delirium, restlessness, muscle twitching and rigidity, with a suggestive Kernig sign. He failed rapidly, and died on this date.

Laboratory Studies.—An electrocardiogram showed a simple tachycardia. The white blood cells varied from 11,000 to 14,000, with an average of 75 per cent

of polymorphonuclear cells. The red cell count was approximately 4,000,000; the hemoglobin was 9.7 Gm. per hundred cubic centimeters. The Wassermann reaction of the blood was negative. Several blood cultures were sterile. The urine was normal at all times. The spinal fluid was normal to all tests. The urea nitrogen of the blood was 7 mg.; sugar, 135 mg.; uric acid, 3.2 mg.

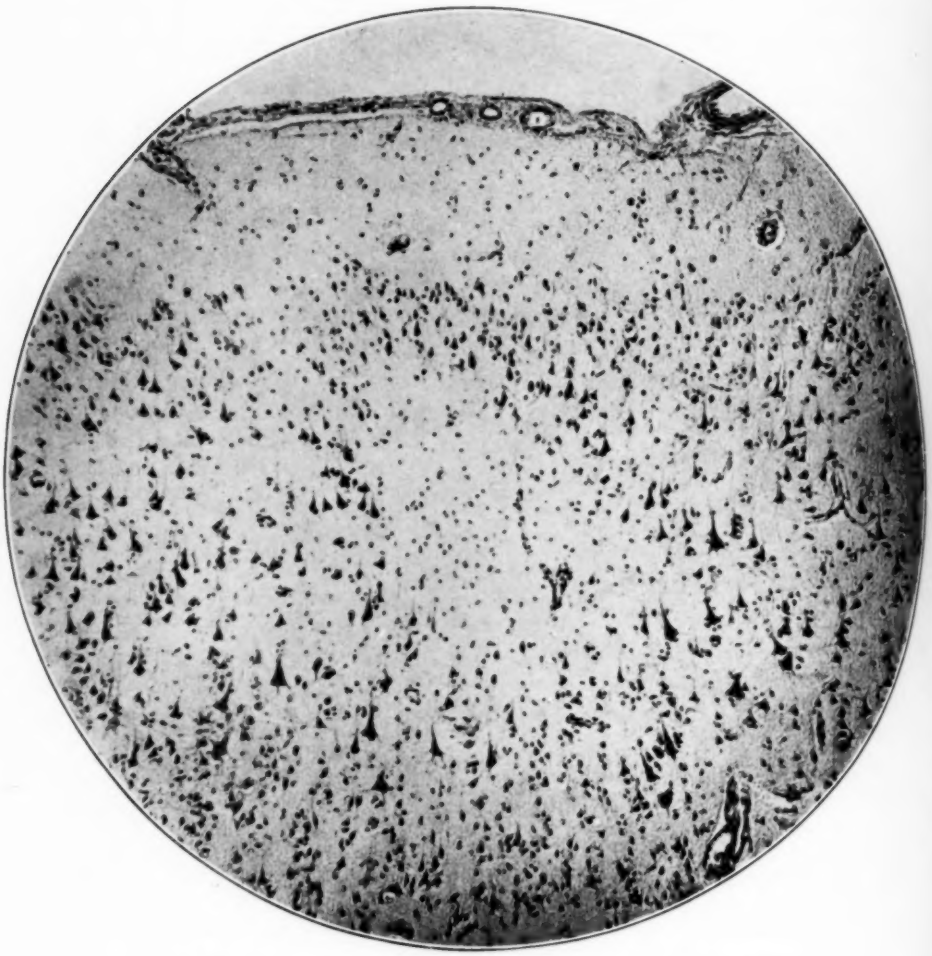

Fig. 2 (case 1).—Verödungsherd of the third cortical layer.

Autopsy.—Macroscopically, the heart showed a myocardial degeneration. The valves were normal. There were: a terminal lobar pneumonia, an acute splenic tumor and congestion, and passive congestion of the kidneys and liver. The stomach and intestines were normal.

Brain: This organ was small, weighing 1,370 Gm. Aside from moderate congestion and edema, there were no other gross abnormalities in the uncut specimen. The ventricular system was undilated. The outstanding feature was the presence of pinhead-sized, petechial hemorrhages, limited to the white matter of

the cerebrum. These were not numerous, from three to five occurring in each section of the brain. The gross diagnosis was "hemorrhagic encephalitis," or purpura of the brain.

Microscopic Examination.—The soft meninges showed mild edema and fibrosis, but without cellular infiltration. The blood vessels were dilated and congested.

Fig. 3 (case 1).—A perivascular verödungsherd is illustrated. Edema of the tissue can be easily recognized by the dilated perivascular spaces.

The cortex exhibited no architectural changes, but the outstanding feature was the prominence of the small vessels. They stood out because of the swelling of their lining cells, hyalinization of their walls and the presence of "Gefässpaketten" or vessel groups (fig. 1). The ganglion cells for the most part showed mild chromatolysis, and only an occasional small "Verödungsherd" (figs. 2 and 3) was uncovered. A uniform mild macroglial proliferation was noted. It was in the subcortex, however, that the small vessels stood out even more conspicuously as

the result of the swelling of the lining cells. Occasionally, petechiae were discovered. For the most part they represented miliary areas of necroses surrounded by microglial accumulations rather than actual hemorrhages. These areas were mostly perivascular, and the central vessel could be found in most of the foci. The changes in the basal ganglia differed in no great respects from those noted in the cortex and subcortex. It is true that the ganglion cells were pale, especially the smaller elements, just as they were in the cortex, but not more so than is seen in the usual case of fever. There was nothing unusual in the rest of the nervous system.

Comment.—In this patient, in an illness lasting seven weeks, with typical polyarthritic manifestations, increased temperature, sweats and prostration, but without chorea, the mental symptoms did not begin until one week before death. This was coincident with the appearance of petechiae on the skin, and it is interesting that the same sort of pathologic change was found throughout the subcortex of the brain. This condition, known as "brain purpura" or "hemorrhagic encephalitis," has been found in relation with other severe infections (Dietrich [22]) and intoxications (Spielmeyer [23] and Schmidt [24]), and is not specific for the rheumatic infection. Its limitation to the subcortex has been commented on by various authors, but without a definite explanation. The cortex itself showed the effects of the prolonged toxemia, with swelling of the cells of the small capillaries and occasional coagulation necrosis and hyalinization of the walls of some of the vessels as evidence of the chronicity of the process.

In the heart itself there was no valvular lesion to explain the very soft systolic murmur at the apex that had been heard during life. It is, therefore, impossible to explain the purpuric spots as an embolic phenomenon; they were probably the result of changes in the vessel walls themselves as a result of the severe toxemia.

CASE 2.—*In a boy, aged 11, who had had polyarthritis, fever and prostration two years previously, there occurred a second similar attack. Mitral and aortic murmurs, with rapidly increasing toxicity and apathy. Choreiform movements, delirium, dyspnea, cyanosis and sudden death. At autopsy, no valvular vegetations; severe edema of the brain, and severe toxic changes of the smaller vessels and cellular elements.*

History.—A. N., an Armenian boy, aged 11, was admitted to the Philadelphia General Hospital, in the service of Dr. J. C. Small, on June 11, 1927, complaining of pain in the joints, fever and sweats. About two years previously, he had had a similar illness which lasted "several" weeks. There was no history of tonsillitis

22. Dietrich, A.: The Origin of Perivascular Hemorrhages in the Brain, Ztschr. f. d. ges. Neurol. u. Psychiat. **68**:315, 1921.

23. Spielmeyer, W.: Histologie des Nervensystems, Berlin, S. Karger, 1922; Infection und Nervensystems, Ztschr. f. d. ges. Neurol. u. Psychiat. **123**:161, 1930; Die zentralen Veränderungen beim Fleckfieber und ihre Bedeutung für die Histopathologie der Hirnrinde, ibid. **47**:1, 1919.

24. Schmidt, M. B.: Ueber Gehirnpurpura und hämorrhagische Encephalitis, Beitr. z. path. Anat. u. z. allg. Path. **7**:419, 1905.

or chorea. The present illness began two weeks before admission with pains in the knees, associated with swelling and heat. The pain then began to shift from joint to joint and finally involved, in addition to the knees, the ankles, shoulders, fingers and elbows. There had been fever and sweats from the onset. The family history was without significance.

Examination.—The boy seemed to be intelligent. He was quiet and appeared toxic. The skin was hot and dry to the touch. The pupils were normal; the tonsils were slightly injected, but no exudate was found. The heart was slightly enlarged. The pulse rate was about 100 per minute, and there was a double murmur at the apex; the pulmonic second sound was accentuated. Only moderate swelling of the joints was present. The temperature was 101 F.

Course.—On June 13, the patient was very toxic, apathetic and mildly delirious. He perspired freely. On the following day, a slight friction sound was heard over the precordium. Very slight choreiform twitching was noted, and there was slightly roughened breathing at the base of the right lung. On June 19, the boy was restless and noisy, and he tossed his head, arms and legs about, with irregular jerkings and twitchings that were suggestive of chorea. The temperature was 102 F.; the pulse rate was 120, and the respiratory rate, 30. The precordial friction sound persisted. On June 21, he suddenly became dyspneic and cyanotic, and the choreiform movements increased. On this day he sat up in bed, asked for water, and suddenly fell back dead.

Laboratory Examinations.—The specific gravity of the urine was 1.020; there was a marked trace of albumin, but otherwise the examination gave negative results. The white cells of the blood numbered 19,500, of which 94 per cent were polymorphonuclears; the hemoglobin was 13.8 Gm. per hundred cubic centimeters. No definite change was shown by the electrocardiogram. Blood cultures were sterile.

Autopsy.—Grossly, the heart showed acute pericarditis with mitral and aortic valvulitis, but no vegetations. There was a rheumatic myocarditis. The lungs showed terminal lobular pneumonia. There was cloudy swelling of the kidneys, and the liver, pancreas and suprarenals were congested and swollen. The large arteries were normal.

Brain: The brain weighed 1,500 Gm., as a result of a tremendous edema. There was marked flattening of the convolutions with obliteration of the sulci. Congestion was likewise more marked than normal. On frontal section, aside from the severe edema and congestion, there were no outstanding features.

Microscopically, the soft meninges showed a rather marked edema with the occasional presence of groups of phagocytic cells (fig. 4), especially in the perivascular regions. The blood vessels were congested and contained numerous polymorphonuclear cells. There were also marked edema and congestion of the blood vessels of the cortex. There was no disturbance of the architecture, but the ganglion cells did not take the stain well. There were no foci of loss of ganglion cells. The most marked feature was the prominence of the small blood vessels, mainly the result of hyalinization of the walls of the vessels and prominence of the lining cells. Nearly all of the blood vessels throughout the cortex were filled with polymorphonuclear cells. The subcortex showed nothing additional. The basal ganglia were not different from the rest of the central nervous system.

Comment.—In this patient the final rheumatic attack was a recurrence; this explains the rheumatic valvulitis of both the aortic and the mitral valves. The attack was typical in all details, and there was a suggestion of choreic manifestations late in the course. Aside from

these, the neurologic picture consisted of a mild delirium without an excessively high temperature.

The outstanding feature in the gross examination of the brain was edema, and this probably is the explanation for the rapid and sudden death in the absence of all embolic phenomena. Microscopically, the

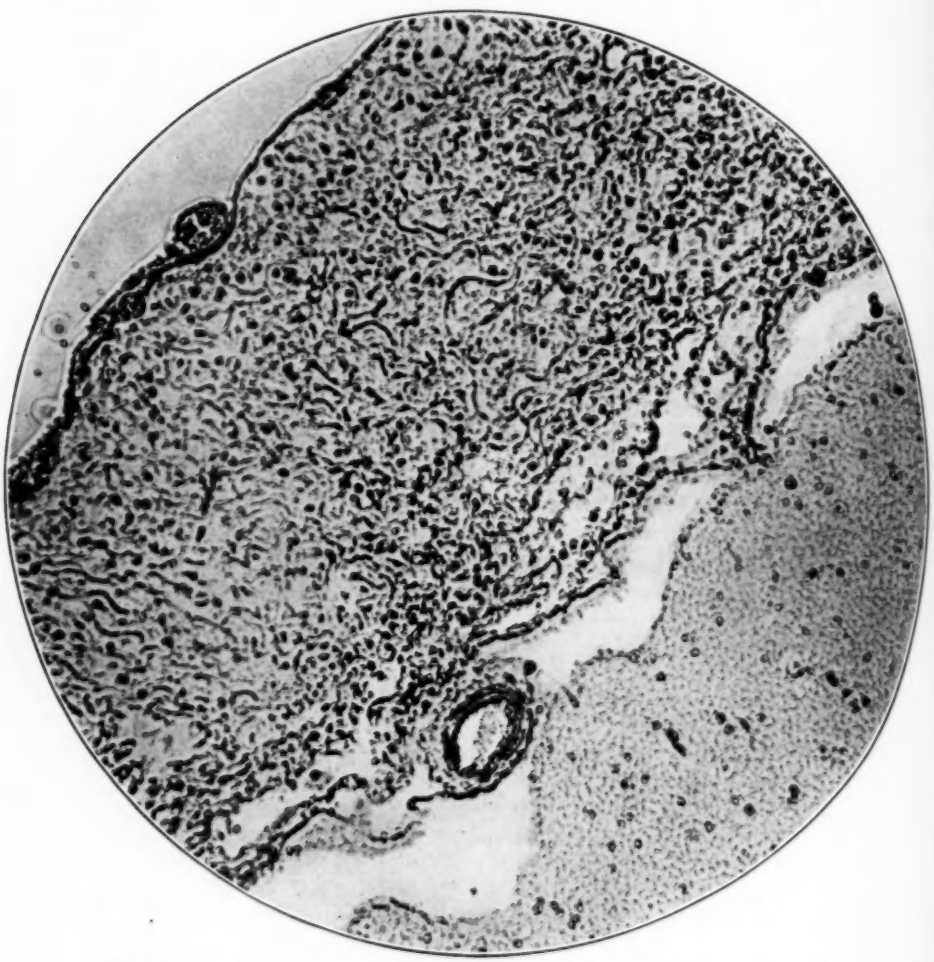

Fig. 4 (case 2).—Intense meningeal dilatation, the result of edema. An occasional phagocytic cell is to be found.

edema and its results were outstanding. It has been shown by Landis [25] that in the presence of anoxemia there occurs a tissue edema in proportion to the decrease of oxygen. The endarteritis of the small vessels may have been either primary, as a result of the infection itself,

25. Landis, E. M.: Micro Infection Studies of Capillary Permeability, Am. J. Physiol. **83**:528, 1928.

or secondary, as a result of the anoxemia. A vicious circle could be established in either case. The choreic manifestations were terminal, and the pathologic changes in the brain were not sufficiently "fixed" to permit definite conclusions.

The severe cerebral edema emphasizes that treatment in these cases should be directed toward relief of this condition. Methods for dehydration, such as the intravenous administration of dextrose or the exhibition of magnesium sulphate by various routes, should be used to combat the edema rather than spinal puncture, which would have a tendency to cause the formation of foraminal herniation. The delirium might be attributed to the edema of the brain rather than to the hyperpyrexia.

CASE 3.—*Illness for four weeks, with polyarthritis, and with systolic mitral murmur. Two weeks later, complete paralysis of the left side, then marked restlessness and death. At autopsy, vegetative endocarditis, a large necrotic area in the right temporal region and marked cerebral edema. Glia-mesodermic nodules in the cortex and basal ganglia.*

History.—F. D., a white girl, aged 9, who was admitted to the Philadelphia General Hospital, in the service of Dr. LaBoutillier, on Oct. 20, 1925, had had pertussis at 15 months, measles at 6 and scarlet fever at 8. The family history was without significance. The present illness began on Oct. 4, 1925, with headache and vomiting, which lasted two days, and joint pains, which were not severe. The headache was continuous. A severe thirst and poor appetite developed. On October 19, the right arm and leg were found to be paralyzed.

Examination.—The child appeared thin, pale and listless. There was paralysis of the left side of the body, including the face. A mitral systolic murmur, with a thrill, was present at the apex of the heart. There was a slight friction sound over the precordium. The abdomen was flat, and the liver was slightly enlarged.

Neurologically, the left pupil was widely dilated and irregular; both pupils reacted to light and in accommodation; a slight nystagmus was present. The left side of the face was smoothed out. A moderate rigidity of the neck was present. The left arm and leg were paralyzed and slightly spastic. The tendon reflexes were not obtained; a Babinski sign and ankle clonus were present on the left; the right side was normal. The child complained of pain in the joints.

Laboratory Examinations.—The urine contained a moderate amount of albumin with hyaline casts and many red blood cells. Examination of the blood showed: red cells, 3,300,000; white cells, 12,500, with 90 per cent polymorphonuclear cells. The Wassermann reaction of the blood was negative. Chemical analysis of the blood revealed 75 mg. of sugar, 14 mg. of urea nitrogen, and 1.2 mg. of uric acid. The temperature ranged from 99 to 101 F.; the respiratory rate was from 20 to 25 per minute; the pulse rate was from 110 to 130.

Course.—The patient grew restless and weaker. A temporary improvement followed spinal drainage—one was done on October 21, and another on October 30. Following this, the condition became progressively worse, and death occurred on Oct. 31, 1925.

Autopsy.—There were: vegetative endocarditis of the mitral valves, acute parenchymatous myocarditis, atelectasis of the lower lobe of the right lung, mul-

tiple anemic infarcts and congestion of the spleen, multiple infarcts in the kidneys, congestion of the liver and perihepatitis, a mild pancreatitis and a simple necrosis of the suprarenals.

Brain: Grossly, the brain was extremely large for a child aged 9 years; it was extremely soft and edematous. In the right temporal lobe was an area

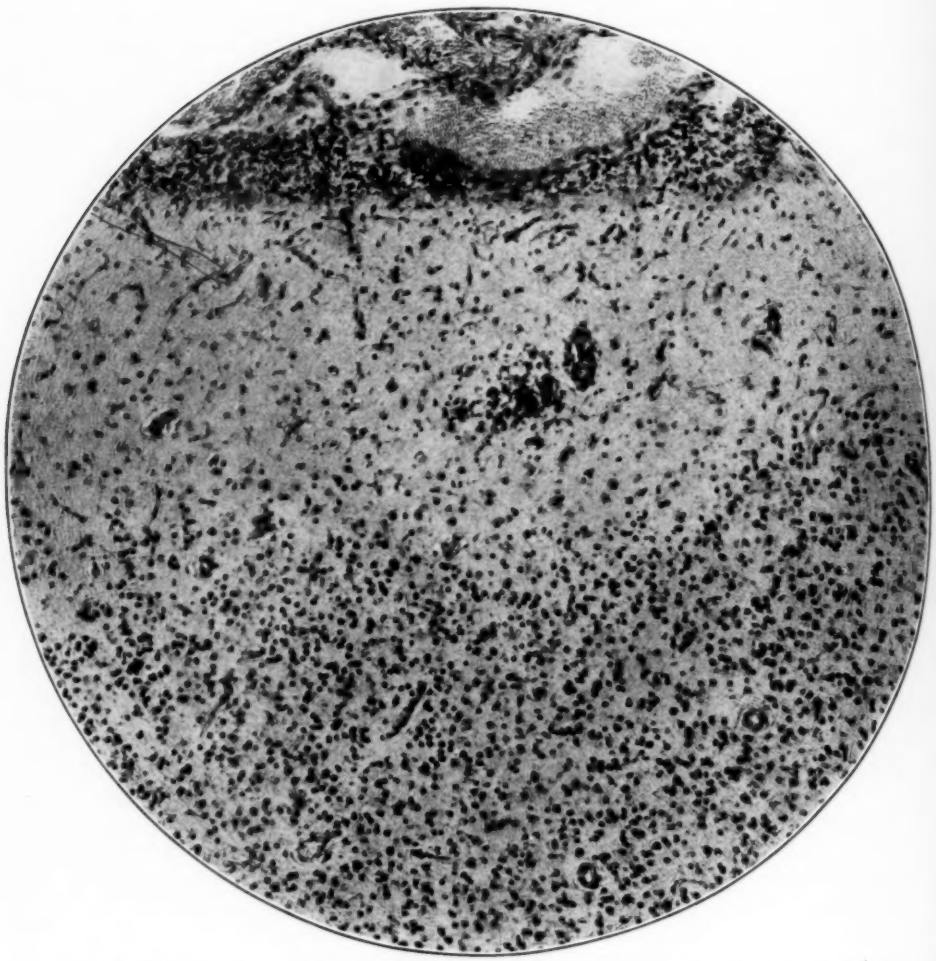

Fig. 5 (case 3).—Meningeal infiltrate consisting mainly of pigment-laden phagocytic cells. The cortex shows a marked glia increase and a glia-mesodermic nodule in the lamina. The small vessels show hyalinization. The capillaries are prominent.

that was poorly defined and was softer than the surrounding tissue; it appeared to be necrotic.

Microscopically, there was a mild yet definite fibrosis and a severe edema of the meninges. In the distended meshes of the subarachnoid space were numerous phagocytic cells (fig. 5).

Cortex: The most evident and uniform change throughout the cortex was edema. Practically every vessel had a marked perivascular space of His, and the ganglion cells had marked pericellular spaces. In portions of the cortex that were relatively well preserved the lamination was normal, but scattered throughout, in no one particular layer, were small nodules exactly similar to those in the temporal

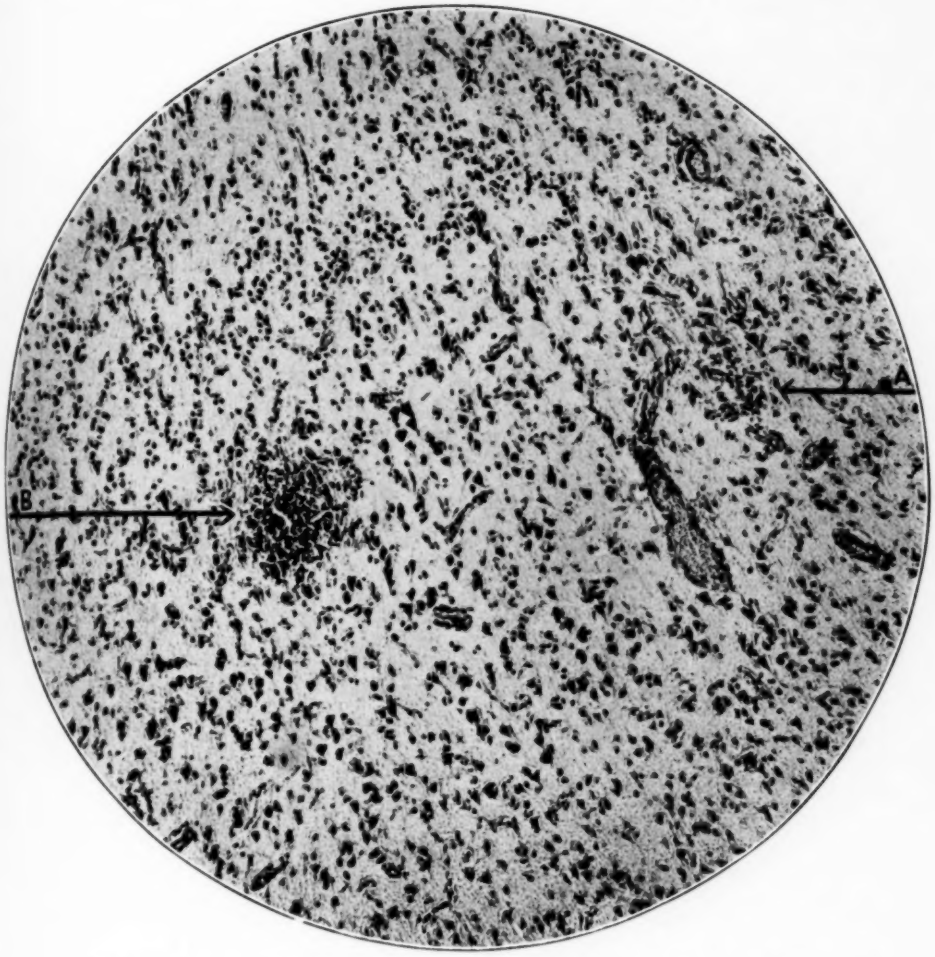

Fig. 6 (case 3).—Glia-mesodermic nodules in the cortex. Focus *A* shows the early stage in the formation of a nodule with central necrosis and gradual mobilization of the glial elements. At *B* is a fully developed glia nodule without a marked reaction on the part of the surrounding tissue. The blood vessels are prominent. There is a mild glia increase in the cortex.

lobe; these will be described later. For the most part the vessels showed thickening of the walls and hyalinization; the glia was definitely increased.

It was, however, in the temporal lobe that the pathologic process was most pronounced. In the area that appeared softened on gross examination, there were an intense edema and a marked disturbance of the lamination because of two fac-

tors: (1) a great loss of ganglion cells, and in some areas no ganglion cells at all, with a beginning increase in glia; (2) numerous "nodules" (fig. 6) throughout both the gray and the white matter. These nodules, as many as from one to two in each low power field, were of two types: (*a*) a nodule that was composed mainly of a central necrotic area surrounded and invaded by polymorphonuclear cells (figs. 7, 8 and 9); (*b*) a nodule that was made up of collections of cells with

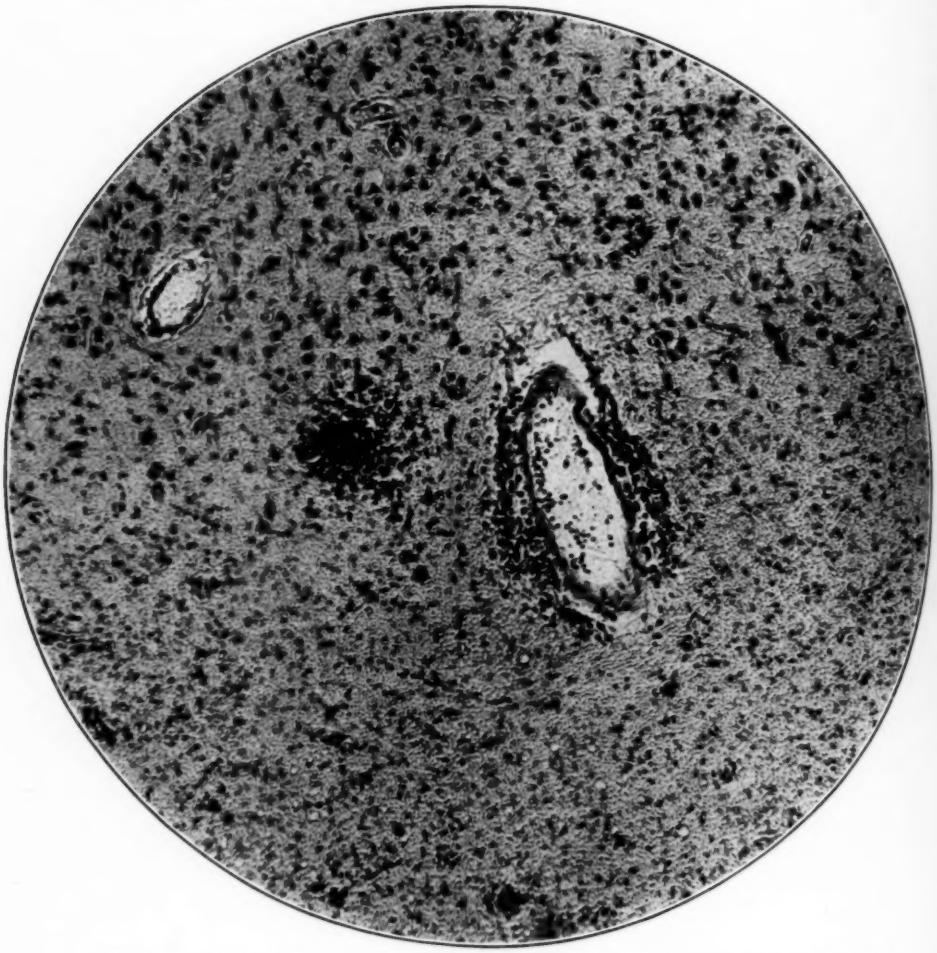

Fig. 7 (case 3).—A glia nodule at the cortical-subcortical margin in relation to a large vessel, showing a perivascular collection of phagocytic elements. Note the intense subcortical gliosis.

small round deeply staining nuclei and well defined and abundant cytoplasm. These foci, for the most part, were around small blood vessels (fig. 10). With differential staining methods, it was found that the major part of the cells making up the nodules were of glial origin, particularly microglia, although there was an occasional cell in which the cytoplasm took the red coloration with the Unna-Pappenheim stain.

There were two other features in the cortex. The more evident was the change in the small blood vessels. Here, in some there was a rather marked swelling and hyalinization of the walls of the small blood vessels (fig. 11); in others there was a proliferative endothelial change (fig. 12), with swelling of the lining cells and new vessel formation. In some vessels there was a combination of the two processes. The second feature was a rather marked glial increase, mainly of the

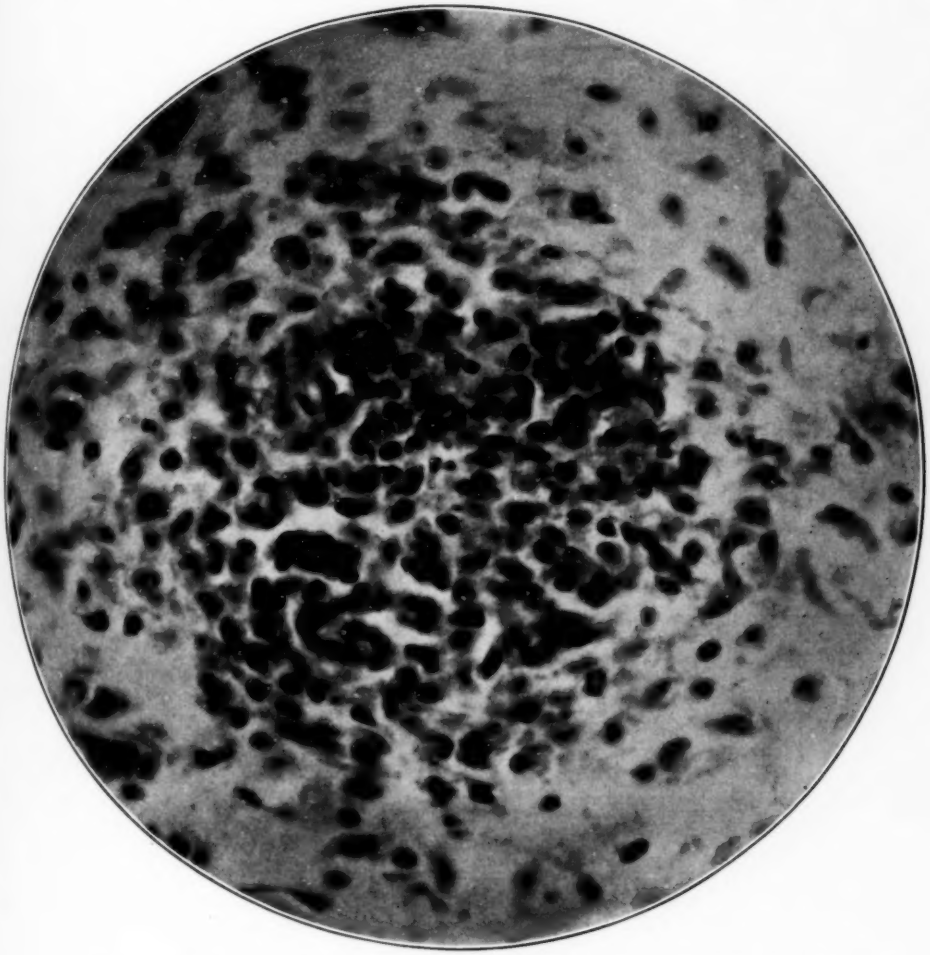

Fig. 8 (case 3).—The nodule in figure 2 under higher power, showing the cellular make-up, mainly glia cells, with an occasional hematogenous element.

macroglia type (fig. 11). There was also a severe ganglion cell degeneration, and in places shadow cells remained (fig. 11).

In the basal ganglia there were very few, widely scattered nodules of the same type as in the cortex. The changes in the small blood vessels were similar in character but much milder in degree.

In the medulla oblongata there were severe edema and moderately severe degeneration of the ganglion cells. Some of the nuclei, especially of the motor cells, showed a marked axonal change. A mild perivascular infiltration of gitter cells was present around some of the blood vessels. Occasional glial nodules, of exactly the same structure as those in the cortex, were scattered throughout the medulla.

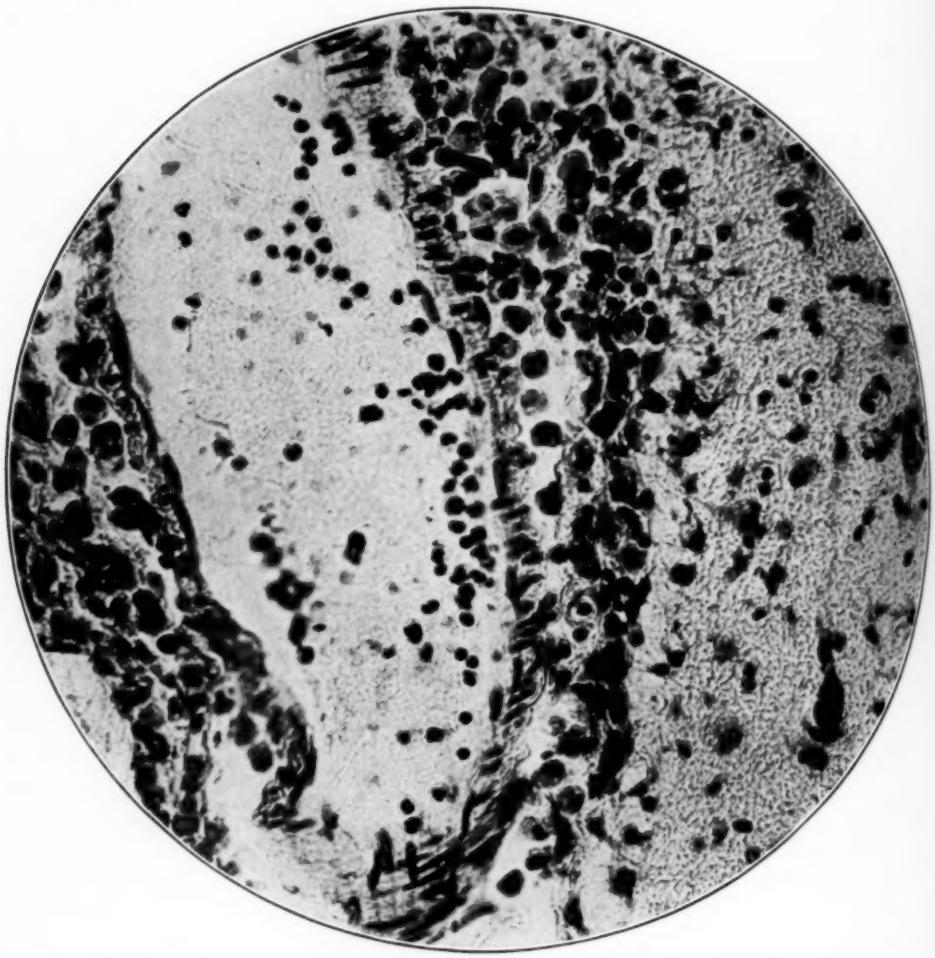

Fig. 9 (case 3).—A perivascular collection of gitter cells (compound granular cells).

Scharlach R stains verified the presence of fat-carrying cells where the nodules were most numerous.

Comment.—Clinically, there was no doubt that this patient had embolic lesions from the heart valves. This would account for the hemiplegia, the gross lesion in the brain and the nodules throughout

the brain. The nodules were very numerous and of a granulomatous nature, similar to those observed in many other conditions. They consisted of areas of necrosis, surrounded and invaded by microglia, at times intermingled with polymorphonuclear cells. These were present not only in the area of gross softening, but also scattered throughout

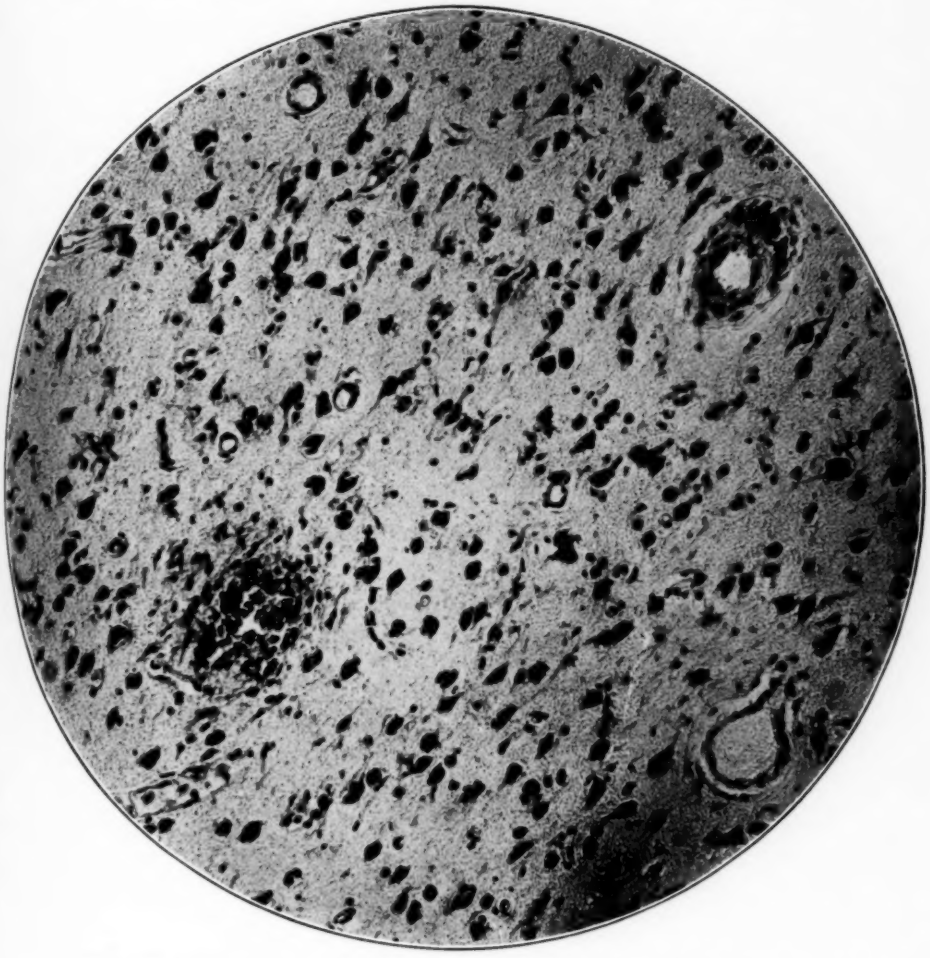

Fig. 10 (case 3).—A glia-mesodermic nodule in the midst of the cortex. The capillaries are prominent because of the swollen intimal cells. The larger vessels have hyalinized walls.

the brain. They were probably areas of embolic necrosis. They were only indirectly related to the rheumatic infection, and the pathologic changes in the brain really represented the results of lesions of the endocardium; for this reason they differed markedly from the changes in the brain in uncomplicated cases of acute rheumatic fever.

Similar changes were noted in the spleen and kidneys in the form of multiple infarcts. These, to our minds, duplicated the changes in the brain.

CASE 4.—*Several months of illness with polyarthritis, fever, delirium and a marked mental depression. Prostration and death, six months after the onset.*

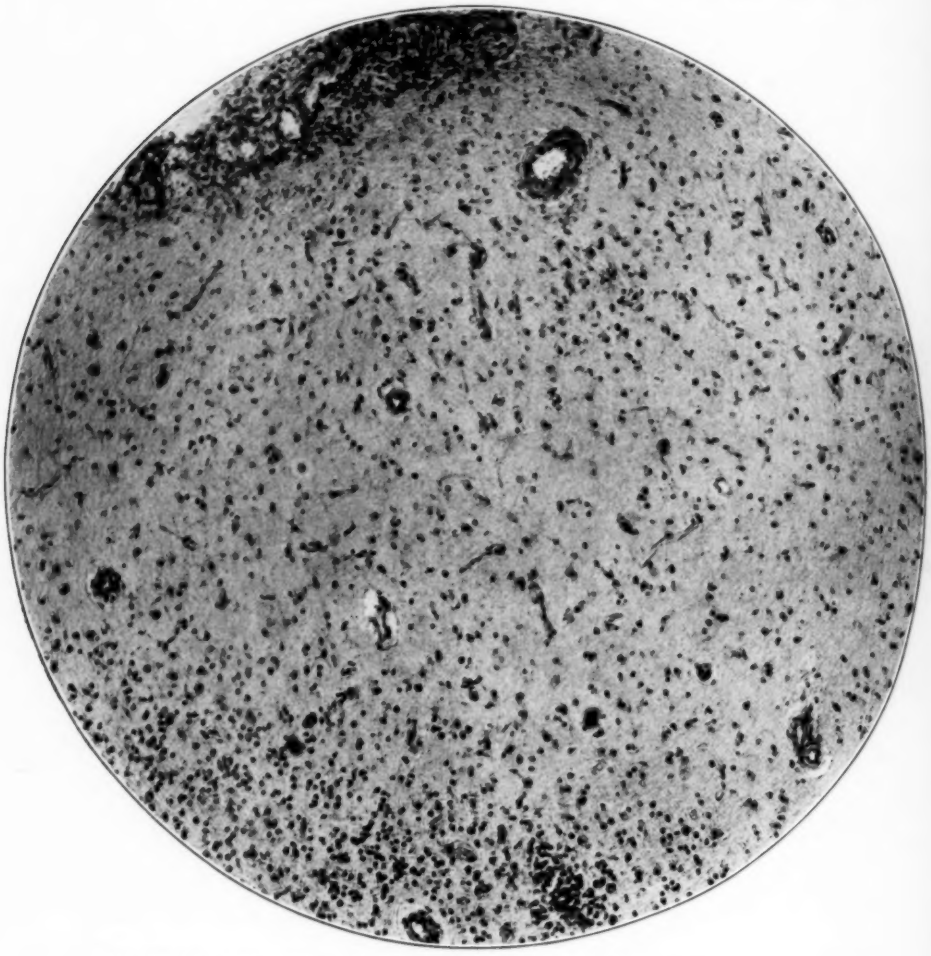

Fig. 11 (case 3).—Changes in the smaller vessels, hyalinization of the medium-sized vessels and prominence of the smaller capillaries. There is meningeal infiltration consisting of phagocytic elements. Intense gliosis of the cortex and loss of ganglion cells are evident.

At autopsy, no valvular vegetations; marked cerebral edema and prominence of the small vessels of the cortex; toxic cell changes throughout the cortex and basal ganglia.

History.—M. S., a white woman, aged 33, was admitted to the Philadelphia General Hospital, in the service of Dr. J. C. Small, on July 13, 1927, after an

attempted suicide. She was born in Germany and came to the United States in 1921. She had had a common school education. She worked as a housemaid until 1915, when she married a man twelve years her senior. They separated in 1924 because of nonsupport and incompatibility. For the past three years she had worked as a housekeeper. Her previous health had been good.

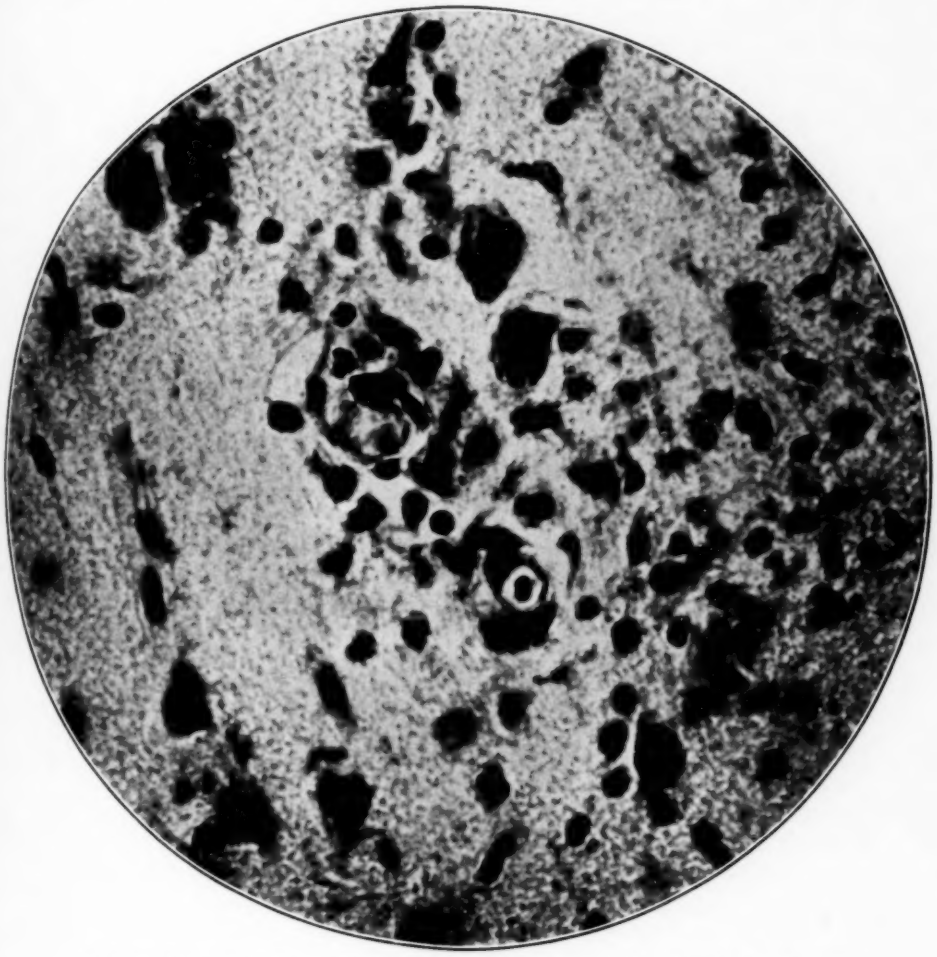

Fig. 12 (case 3).—Two small capillaries cut transversely, showing the tremendous swelling of their lining cells.

In January, 1927, there developed pain, redness and swelling of the right hip, knee, elbow and shoulder, and of the small toe and finger joints. The condition had spread from joint to joint and was associated with high fever and delirium. She was in bed for ten weeks. After getting up, she did light housework, but began to lose weight and strength. She then began to worry; the joints began to swell, and the pain returned whenever she exposed herself to dampness or cold air. This caused her to cry and become depressed. Six weeks before admission, she

became more despondent because her child developed scarlet fever. She feared that the police were after her with the purpose of killing her. On July 1, 1927, twelve days before admission, she prepared her home for the child who, she believed, was dead. She then changed her mind and went to New York, where she was taken to Bellevue Hospital for observation. There she maintained that she saw a big parade of airplanes; she saw her sister dancing outside the window, and feared that she was to die. She attempted suicide by drinking an antiseptic solution. During all this time, the joints continued to swell and were painful. She was returned from Bellevue Hospital to Philadelphia, and was admitted to the Philadelphia General Hospital. On admission, she showed mental retardation and did not speak. She sat dejected, moaned and had to be fed by spoon.

Examination.—The tonsils were small and ragged, but showed no exudate. There were no audible heart murmurs, but the muscle tone was poor. The blood pressure was 140 systolic and 90 diastolic. The lungs and abdomen were normal. There was moderate swelling of most joints.

Laboratory Examinations.—The urine contained a trace of albumin and hyaline casts. Examination of the blood showed: red cells, 3,000,000; white cells, 11,400, with 77 per cent polymorphonuclear cells, 21 per cent lymphocytes and 2 per cent eosinophils. The Wassermann reaction of the blood and spinal fluid was negative. The urea nitrogen of the blood was 15 mg.; the sugar, 71 mg.

Course.—Antirheumatic remedies were administered, but the patient did not respond; she grew steadily worse. During her stay in the hospital the temperature ranged from 100 to 101 F.; the pulse rate varied from 120 to 150; the respiratory rate was from 20 to 22. The patient's condition failed rapidly, and she died on July 31, 1927.

Autopsy.—There were: diffuse endocarditis and myocarditis, but no vegetations on the valves; moderate atheroma of the aorta; terminal lobular pneumonia, with marked congestion and edema; chronic glomerular nephritis and acute parenchymatous degeneration of the kidneys; fatty degeneration of the liver, and congestion and slight enlargement of the spleen.

Brain: Grossly, the brain was small and somewhat soft; it weighed 1,300 Gm. A mild convolutional atrophy was present, but was not striking because of edema of the overlying meninges. The blood vessels at the base were small, bluish and collapsed, and showed no sclerotic changes. There was generalized congestion. On frontal section, the only features of note were the prominence of the dilated and congested small vessels, and a fairly intense edema. There were no ventricular dilatation or gross lesions within the brain substance.

Microscopically, the soft meninges showed wide separation as the result of edema within the subarachnoid space. Within the distended meshes were large endothelial cells, as well as pigment-laden phagocytic cells and an occasional clump of round cells of the lymphocytic type.

In general, there was a normal architectural arrangement of the cortex, with the usual number of ganglion cells. There were, however, occasional areas of incomplete softening (Verödungsherde), with loss of ganglion cells, increase in glia and in some a feeble effort at repair and vascularization. The areas of Verödung, or devastation, contained no gitter cells and had not provoked a reaction of the surrounding tissues. They were, however, by no means frequent and had to be diligently sought. They favored no particular area or areas, but were scattered haphazard through the cortex. The condition of the small blood vessels was noteworthy. For the most part the small vessels stood out because of thickening and hyalinization of their walls. In the usual toluidine blue preparations of

alcohol-fixed material, the nonstainability of the walls of the vessels stood out in marked contrast to the blue color of the cellular elements. In the rest of the small vessels there was a moderate swelling of the lining cells, but rarely budding. These changes in the small vessels probably explain why the "Verödungsherde" appeared older than the foci usually seen in cases in which death occurred earlier in the disease. It must be stressed that these changes were found not only in the cortex and subcortex, but also, in exactly the same degree, in the subcortical ganglia.

As a rule, the ganglion cells were uniformly paler than is considered normal, but probably not more so than is seen in most cases in which an infection or toxemia has been present for some time prior to death. It should be noted that the ganglion cells in the basal ganglia were not affected to a greater degree than those in the cortex. It is true that neuronophagia was more frequent in the subcortical ganglia than in the cortex, but this is usual in cases without symptoms in the brain, as was pointed out long ago by Bielschowsky.[26] In the subcortical white matter, even in the ordinary toluidine blue preparations, there were perivascular accumulations of pigment-laden phagocytic cells. In the fat preparations this was verified by the finding of gitter cells within the Virchow-Robin spaces.

Throughout the brain, more or less uniformly, edema requires special mention. Most of the older pathologists believed that edema of the brain was more easily recognized grossly than microscopically. By a comparison of hydrated with dehydrated brains of animals Kubie[27] showed the importance of the pericellular spaces and the perivascular spaces of His, both of which were formerly considered to be artefacts. Fixation must be carefully done in the graded alcohols, and celloidin must be used for embedding in order to make a proper interpretation of this finding. Paraffin-embedded preparations cannot be used to make a diagnosis of edema of the brain.

Comment.—In this case there was a history of a long-standing acute rheumatic fever and a mental disorder that lasted to the time of death. It might be argued that the acute rheumatic fever was only an episode in the life history and that a depression would have developed under the influence of other precipitating factors. At the time of admission to the hospital, inflammatory changes in the joints were still present, and there was an elevation of temperature and of pulse rate. The heart showed endocardial and myocardial changes such as are seen in other cases of acute rheumatic fever. Pathologically, in the brain there were the results of an old edema with changes in the cortex, as shown by comparatively old, widely scattered scars. With these areas of degeneration, the walls of the small blood vessels showed the hyalinization that is evidence of the comparative chronicity of the process. A diffuse degeneration throughout the white matter was demonstrable.

We are not attempting to describe in this case a mental picture of depression as the result of the microscopic picture that was observed.

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26. Bielschowsky: Beitrage zur Histopathologie der Ganglionzelle, J. f. Psychol. u. Neurol. **18**:513, 1911.

27. Kubie, L. S.: Changes in Intracranial Pressure During Forced Drainage of the Central Nervous System: The Hydration Factor, Brain **51**:244, 1928; Intracranial Pressure Changes During Forced Drainage of the Central Nervous System, Arch. Neurol. & Psychiat. **16**:319 (Sept.) 1926.

The case is one, however, of a patient in whom depression occurred and in whom we have found a definite pathology. That the two are related cannot be admitted, nor can it be denied.

CASE 5.—*Acute rheumatic fever, followed by chorea, lasting several weeks, at 13. In a second attack, choreiform movements for one week, followed by polyarthritis, fever and sweats. Double aortic murmur; later, auricular fibrillation and death. At autopsy, no valvular vegetations; toxic cellular changes throughout the cortex and basal ganglia; prominence of the small vessels and many "Verödungsherde."*

History.—R. G., a white girl, aged 17, was admitted to the Philadelphia General Hospital, in the service of Dr. A. A. Stevens, on March 29, 1929, complaining of soreness all over the body. The early history was without importance. At 13, she had an acute illness, with fever, sore throat, sweating and pain in all joints. She was in bed for several weeks. This was followed by an attack of acute chorea, which also lasted several weeks. The present illness began six weeks before admission with sore throat and slight choreiform movements, which did not last more than one week. Three weeks later, she was confined to bed with chills, fever, pain in the joints and a stiff neck. There was profuse sweating, with palpitation of the heart and dyspnea.

Examination.—The head was essentially normal; the cranial nerves were normal. The neck was painful on motion and was rigid. There were a few hard, discrete lymph nodes about the neck. There were a presystolic rumble, ending in a crescendo in the first sound, and a slight enlargement of the heart to the left. The blood pressure was 122 systolic and 70 diastolic. The lungs and abdomen were normal. All of the large joints were tender on motion and slightly swollen.

Laboratory Studies.—The urine contained a marked trace of albumin, with granular and hyaline casts and many leukocytes. Examination of the blood showed: red cells, 3,720,000; white cells, 13,900, with 87 per cent polymorphonuclear cells. A blood culture was negative. The feces contained no ova. The Wassermann reaction of the blood was negative.

Course.—On March 11, her physician had noted a double aortic murmur. The joints improved somewhat under treatment, but the dyspnea and the cardiac impairment continued. On March 31, there was severe dyspnea, and a cardiogram showed auricular fibrillation. The patient's condition failed rapidly, and she died on that day.

Autopsy.—There were: obliterative pericarditis; chronic mitral and aortic endocarditis of rheumatic type, without vegetations; chronic diffuse myocarditis; left lung, normal; terminal bronchopneumonia in the right lung; cloudy swelling and passive congestion of the liver, kidneys and spleen; a few anemic infarcts in the spleen, and a normal aorta. Blood cultures remained sterile.

Brain: Grossly, the brain was unusually small, weighing only 1,220 Gm. There were no unusual edema or congestion and no gross lesions of any sort. Microscopically, the meninges showed moderate fibrosis, with only slight edema and without inflammatory manifestations. The large vessels showed absolutely no changes. The small blood vessels, especially those in the cortex, were very prominent because of swelling of the intima and hyalinization of the vessel walls. For the most part the normal architectural arrangement in the cortex was maintained, but scattered about were small areas where the ganglion cells had disappeared and only glial scars remained. These were the typical "Verödungsherde" that are met with so frequently in other toxic and infectious conditions. They involved, for the most

part, the second and third cortical layers, but were not entirely limited to them. The basal ganglia showed the same type of changes, but to a much less degree.

Comment.—In this case there was an attack of acute rheumatic fever followed by Sydenham's chorea, four years before the present attack. The terminal illness lasted in all about six weeks, and began with rheumatic manifestations as well as slight choreiform movements, which did not persist.

At autopsy, obliterative pericarditis and chronic valvulitis without vegetations were present. The absence of edema of the brain must be considered in relation with the absence of delirium or signs of increased intracranial pressure. The hyalinization of the small vessels probably attests the fact that there had been a former severe infection. The presence of endarteritis of the small vessels bears testimony to the infection at the time of death. There were no embolic lesions. The relationship of the older lesions in the basal ganglia to the previous chorea is problematic.

GENERAL COMMENT

We have described five cases of rheumatic infection with clinical histories and physical findings typical of that condition. Since the brain is not an isolated organ but takes part in the same pathologic processes to which the rest of the body is subject, it was no surprise to find that the same general type of involvement was present in the brain as has been described in the rest of the body (von Glahn and Pappenheimer, quoted by Dietrich,[22] Sachs,[10] Swift,[1] Klinge[28] and Klotz[29]). It is true that we found no Aschoff bodies or the so-called specific lesion of acute rheumatic fever in the brain, but this lesion has been described only in the heart and blood vessels (Clawson[30] and von Glahn and Pappenheimer[9]). There has, therefore, been no great difference in the brain in acute rheumatic fever from that in any other general infection. There is nothing specific about the condition in the brain to lead one to suspect that acute rheumatic fever had been present during life. There is, however, one great difference that must be stressed: the tendency to the production of an endocarditis in acute rheumatic fever of a vegetative character (Swift[1]), and the consequence of the embolic phenomena that can result from loosening of the small particles on the cardiac valves. This complication is well illustrated

28. Klinge, F.: I. Das Gewebsbild des fieberhaften Rheumatismus (Frühinfiltrat), Virchows Arch. f. path. Anat. **278**:438, 1930; II. Das Substrat-chronische Stadium des Zellknötchen, ibid. **279**:1, 1930; III. Narbe und Rezidiv, ibid. **279**:16, 1930.

29. Klotz, A.: Rheumatic Fever and the Arteries, Tr. A. Am. Physicians **17**:181, 1912.

30. Clawson, B. J.: The Aschoff Nodule, Arch. Path. **8**:664 (Oct.) 1929.

by case 3, in which gross damage to the brain probably resulted from such embolic particles.

It has been claimed that the mental symptoms particularly, such as restlessness, delirium and actual mental abnormalities, were the result of the marked hyperpyrexia (McCrae [31] and Targowla [32]) that may occur in acute rheumatic fever. The effect of different degrees of temperatures on the brain is now fairly well known in view of the frequency of diathermic treatment for dementia paralytica and other conditions of the nervous system. C. Neyman, in a personal communication, stated that, in normal persons in whom fever is artificially produced, at 102 F. there is a feeling of impending danger; at 102.5 F., the sensation of a desire to run away; at 103 F., the patients become quiet; from 103 degrees to 103.5 F., they become somnolent, but they feel well again at 105 F.; at from 106 to 107 F., they become comatose. While hyperpyrexia does occur in acute rheumatic fever, it is of interest that in none of our cases was there a temperature in excess of 104 F., so that the mental and nervous manifestations could not be traced directly to the increase in the temperature itself. It is well known that in many toxemias, without an increase of the temperature at all, there occurs the same type of clinical reaction as was seen in our patients.

In only one was there a permanent mental picture, although it must be stated that the rest of our patients probably did not live long enough for mental symptoms to develop. We believe that the permanent picture in the one case might be explained by the fact that there were areas of destruction in the brain in the form of so-called "Verödungsherde." While in this patient there were factors of intense stress and strain, still the histologic finding in the brain would suggest to us symptoms of a more or less permanent organic nature. It must be mentioned at this point, in reference to this patient, that there were no vegetations on the cardiac valves, so that it is impossible to attribute the areas of coagulation necrosis to embolic phenomena.

The most uniform finding in the brains in our five cases, aside from the cloudy swelling that one meets with all over the body in any infection, was the productive endarteritis of the small cortical vessels. This condition, known since 1904, when attention was first called to it by Nissl [33] and Alzheimer [34] in syphilis under the name of "Endarteritis

31. McCrae, T., in Osler, William: System of Medicine, Philadelphia, Lea & Febiger, 1913, vol. 1, p. 992.

32. Targowla, René: Le rhumatisme cérébral d'emblée, Presse méd. **37**:572, 1929.

33. Nissl: Zur Histopathologie der paralytischen Rindenerkrankungen, in Histologische und histopathologische Arbeiten über die Grosshirnrinde, Jena, Gustav Fischer, 1904.

34. Alzheimer, A.: Progressive Paralyse und endarteritische Hirnlues, Centralbl. f. Nervenh. **16**:442, 1905.

Syphilitica of the Small Cortical Vessels," has been described in many other conditions since that time. Experimentally and clinically, it has been found in poisoning with the heavy metals and in various infections and toxemias (lead: Bonfiglio,[35] Jores, [36] Mott [37] and Hassin; [38] arsphenamine: Weygandt and Jakob and Kofka; [39] manganese: Lewy and Tiefenbach; [40] carbon monoxide: Herzog [41] and Stewart; [42] typhus: Spielmeyer and Hassin; [38] malaria: Cerletti [43]).

The occurrence of edema in four of five cases is worthy of note. Edema of the brain has recently assumed greater importance in view particularly of the work of Kubie,[27] who showed that even microscopically there is a distinction between a hydrated and a dehydrated brain. All our work in these cases was done on material that had been fixed in graded alcohol and embedded in celloidin. It was therefore easy to compare the perivascular and pericellular spaces in them with comparatively normal cases. It was soon evident that the dictum of even recent pathologists was not correct in asserting that edema of the brain was more easily recognizable grossly than microscopically. We found in our cases that the pericellular spaces and the perivascular spaces of His were not artefacts, but that their size was in direct relation to the amount of edema present.

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35. Bonfiglio, F.: Circa la allerazioni della cortecia cerebrale consequenti ad intossicazione sperimentale da carbonate di plombo, in Nissl: Histlogische und histopathologische Arbeiten über die Grosshirnrinde, Jena, Gustav Fischer, 1909, vol. 3, p. 359.

36. Jores, L.: Ueber die pathologische Anatomie der chronischen Bleivergiftung des Kaninchens, Beitr. z. path. Anat. u. z. allg. Path. **31**:183, 1902.

37. Mott, F. W.: Examination of the Nervous System in a Case of Chronic Lead Encephalitis, Arch. Neurol. & Psychiat., London **4**:117, 1909.

38. Hassin, G. B.: The Contrast Between the Brain Lesions Produced by Lead and Other Inorganic Poisons and Those Caused by Epidemic Encephalitis, Arch. Neurol. & Psychiat. **6**:268 (Sept.) 1921; Brain Changes in Typhus Fever Contrasted with Those in Epidemic Encephalitis and Acute Poliomyelitis, ibid. **11**:121 (Feb.) 1924.

39. Weygandt, T. W.; Jacob, A., and Kofka, A.: Klinische und experimentelle Erfahrungen bei Salvarsan Injektionen in dem zentral Nervensystem, München. med. Wchnschr. **61**:1608, 1914.

40. Lewy and Tiefenbach: Experimentelle Manganperoxyd Encephalitis und ihre sekundäre Autoinfection, Ztschr. f. d. ges. Neurol. u. Psychiat. **71**:303, 1921.

41. Herzog, G.: Zur Pathologie der Leuchtgasvergiftung, München. med. Wchnschr. **67**:558, 1920.

42. Stewart, R. M.: Cortical Changes in Carbon Monoxide Poisoning, J. Neurol. & Psychopath. **1**:125, 1921.

43. Cerletti, N.: Die histopathologischen Veränderungen der Hirnrinde bei Lamaria perniciosa, in Nissl: Histologische und histopathologische Arbeiten über die Grosshirnrinde, Jena, Gustav Fischer, 1911, vol. 4, p. 169.

The effect of edema needs special mention. Since the recent introduction of dextrose intravenously for the control of edema of the brain, we have at times seen startling clinical improvement by the relief of cerebral edema. As the result of this therapeusis, instead of being semistuporous and delirious, the patient becomes mentally clear and alert. It has been shown experimentally that with edema there necessarily results a lessening in the blood supply of the brain, which leads at times to even greater outpouring of fluid into the tissues. Unless relieved, a vicious circle may be initiated. This would give an indication in cases of this sort for the relief of the intracranial pressure. It might be argued that the spinal fluid pressure as measured with a manometer may show no abnormal elevation. It is true that a tremendously swollen brain, with consequent marked lessening in the amount of cerebrospinal fluid, may give no indication of the abnormal pressure of the elements of the brain by manometric reading. This is seen particularly in the alcoholic wet brain, and in similar conditions. Here, greater relief can be afforded by the intravenous administration of dextrose than by spinal drainage, and without the danger of foraminal herniation.

In only two of our cases were there choreiform movements. The subject of the causation of these movements would take us too far afield, but suffice it to say that Lhermitte and Pagniez [14] expressed themselves as unable to conceive of choreic movements without cooperation of the cortex, but they did not agree with Wilson [44] that cortical lesions must exist. In our two cases there was nothing unusual about the basal ganglia to account for the terminal chorea, except possibly the acellular foci in one of them. It is true that in all of our cases there was a fairly uniform involvement of the brain, and it was difficult to state what part was most affected. Not knowing which cases had shown chorea we could not have picked them out. Neuronophagia in the basal gray nuclei is no index of abnormality. It must be stressed that inflammatory manifestations were lacking.

One of the important findings in these cases concerns the blood vessels. As a rule, the large vessels remained relatively unaffected, but the changes in the small vessels were of two kinds: (1) An acute and recent change, with swelling and proliferation of the lining cells and at times with new vessel formation. This is the same type of change that one sees in the acute stages of syphilis. (2) Thickening and hyalinization of the walls. This appears to be a later change and to result, according to Hueck,[45] from a colloid disorganization of the con-

44. Wilson, S. A. K.: Disorders of Motility and of Muscle Tone, Lancet **2**: 169, 215 and 268, 1925.

45. Hueck: Anatomisches zur Frage nach Wesen und Ursache der Arteriosklerose, München. med. Wchnschr. **67**:535, 1920.

nective tissue that begins with a separation of the intimal vessel layers outside of the endothelium by the tissue fluids and then a coagulation of its albuminous content. This is the type of vessel change that predominates in the relatively long-standing cases, although it may appear within the first week. It is the characteristic change in chronic toxemias, as in tuberculosis (Askanazy [46]) and pellagra (Winkelman [47]) and was seen by us [48] in one case of chorea of pregnancy of six months' duration. To us this one finding has been an index of a moderate chronicity.

The changes in the meninges in our cases have tended toward a so-called "serous meningitis," with at times a moderate increase in the fluid and an outpouring of degenerative material from the brain, which may be picked up by the macrophages of the reticulo-endothelial system. This is the type of reaction that one meets within any mildly degenerative conditions of the central nervous system.

The changes in the ganglion cells were by no means specific. They were the same as many have found in toxic and infectious conditions, and conformed to the cloudy swellings of other tissues of the body.

The nodules seen in case 3 belong to the granuloma group in which the center was originally an area of necrosis, about which there soon occurs a ring of small glia nuclei, most of which are microglia, at times interspersed with polymorphonuclear cells. Similar nodules have been seen in many other conditions: pernicious anemia (P. Schröder [49]); malaria (Dürck [50]); typhus (Hassin [38]), and epidemic encephalitis (Stern [51]). Very rarely, however, have there been as many nodules as in our cases.

CONCLUSIONS

1. Acute rheumatic fever does not produce in the brain a specific change that can be recognized either grossly or microscopically.

2. The changes that are present in the brains of patients who have shown neurologic and psychiatric symptoms during the course of acute rheumatic fever are similar in every way to the changes that occur in any other acute infection and toxemia.

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46. Askanazy, M.: Die Gefässveränderungen bei der akuten tuberkulösen Meningitis und ihre Beziehungen zu den Gehirnläsionen, Deutsches Arch. f. klin. Med. **99**:333, 1910.

47. Winkelman, N. W.: Neurohistopathology of Pellagra, Ztschr. f. d. ges. Neurol. u. Psychiat. **102**:38, 1926.

48. Winkelman, N. W., and Eckel, J. L.: Endarteritis of the Small Cortical Vessels in Severe Infections and Toxemias, Arch. Neurol. & Psychiat. **21**:863 (April) 1929.

49. Schröder, P.: Grosshirnveränderungen bei perniziöser Anämie, Monatschr. f. Psychiat. u. Neurol. **35**:543, 1914.

50. Dürck: Ueber die bei Malaria pernicioso comatosa auftretenden Veränderungen des zentral Nervensystems, Arch. f. Schiffs- u. Tropen-Hyg. **21**:117, 1917.

51. Stern, F.: Die epidemische Encephalitis, Berlin, Julius Springer, 1928.

3. The rôle that edema of the brain plays in the production of symptoms of so-called cerebral rheumatism has probably been greatly underestimated. Unless relieved, a vicious circle may be initiated.

4. The endarteritis of the small vessels, which has been found in every case, has probably two causations: (*a*) purely mechanical, as the result of edema of the brain; (*b*) toxic irritation through the blood stream.

5. Areas of Verödung, or acellular areas, in the brain are found frequently in cases of acute rheumatic fever, as they are in other infections and toxemias, and may produce a permanent clinical picture if sufficiently numerous.

6. The occurrence of endocarditis can completely change the picture in the brain. Here the effect of embolic phenomena must be kept in mind.

7. Purpura of the brain is a possibility, and may give evidence of its occurrence by similar lesions in the skin.

SENSORY CORTICAL AREA

AN EXPERIMENTAL ANATOMIC INVESTIGATION

E. C. MILCH, M.D.
NEW YORK

In 1924, Dusser de Barenne [1] described a rather large area of the brain of Macacus, any small part of which, when poisoned by strychnine, caused changes in sensation in the heterolateral and in the ipsolateral sides of the body. In an endeavor to find some anatomic basis for this physiologic fact, at the suggestion of Professor A. Jakob I operated on a series of monkeys' brains and studied the degeneration caused by small cortical excisions within this area. Although Dusser de Barenne's work had been done on Macacus, I selected Cercopithecus, the brain of which is morphologically almost similar to that of Macacus, because this species of monkey was considerably cheaper in Hamburg at the time the work was done.

The sensory field of Dusser de Barenne corresponds exactly with areas 1 to 3, 4, 5, 6 and 7 of Brodmann,[2] except the medial surface of the hemispheres, on which Dusser de Barenne did not experiment. In my work it was thought best to confine the studies to a few fields, and to repeat the experiments rather than to work on more fields and not have the results controlled.

For purposes of orientation, Dusser de Barenne's illustration of his fields in Macacus (fig. 1) and Vogt's [3] chart of cortical areas in Cercopithecus (fig. 2) are reproduced.

TECHNIC

Under ether anesthesia, various portions of the skull were opened, the dura was incised and retracted and a piece of the cortex was excised, an attempt being made to injure as little of the white matter as possible. Bleeding was controlled; the dura was then sewed back, and the scalp flap was closed. In each case the animal was allowed to live for eleven days; it was then killed, and the brain was removed and treated according to the Marchi technic. Frontal serial sections of the brains were made, and the degeneration was observed microscopically. Despite the errors

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From the neuropathologic laboratory of Professor Dr. A. Jakob, Hamburg-Fredrichsberg, Dr. Weygandt, director.

1. Dusser de Barenne, J. G.: Proc. Roy. Soc., London, s. B, **96**:272, 1924; Deutsche Ztschr. f. Nervenh. **83**:273, 1924.

2. Brodmann: Vergleichende Lokalisationslehre der Grosshirnrinde, Leipzig, Johann Ambrosius Barth, 1909.

3. Vogt: J. f. Psychol. u. Neurol. **25**:439, 1919.

prone to appear under the Marchi technic, as pointed out by Duncan,[4] I believe that the observations recorded mirror the facts.

In the accompanying illustrations (figs. 3, 4, 5, 6 and 7) the large black spots indicate the excised areas and the small dots indicate the relative number of degen-

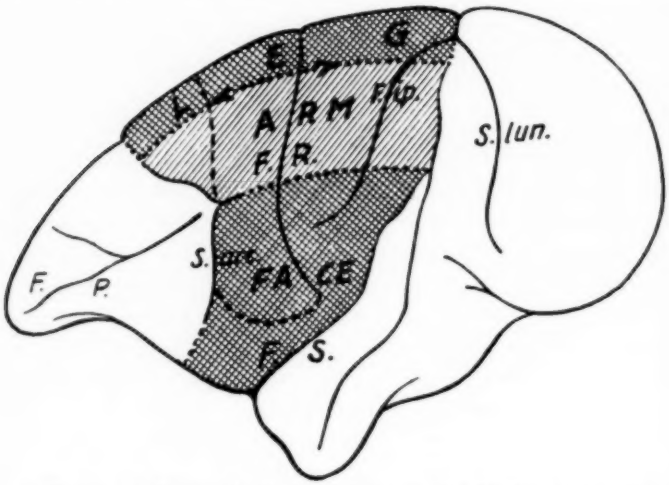

Fig. 1.—Dusser de Barenne's diagram showing distribution of the sensory fields in Macacus.

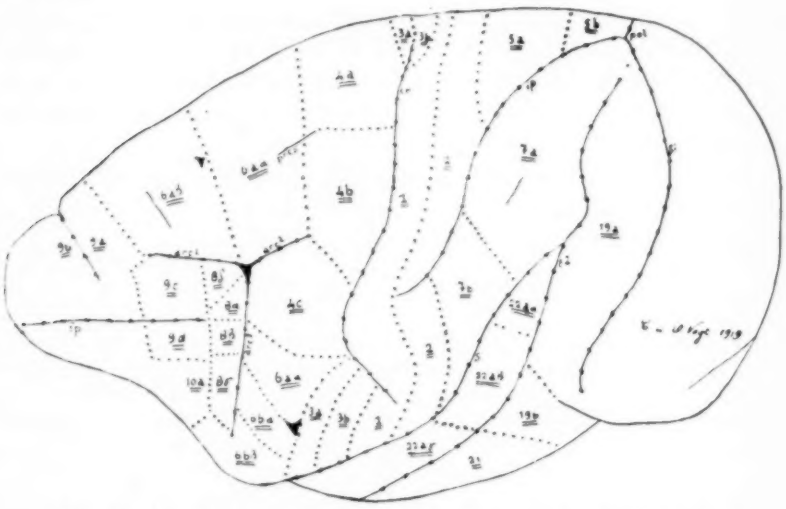

Fig. 2.—Vogt's diagram showing cortical areas in Cercopithecus.

erated fibers going to that cortical area via the subcortex. Because I considered that the observations on intracortical connections were doubtful, they are not included in the following résumé. Other paths of degeneration, as noted, are included in the report. All operations were performed on the left hemisphere.

4. Duncan, D.: Marchi Method; Discussion of Some Sources of Error and Value of the Method for Studying Primary Changes in Myelin Sheath, Arch. Neurol. & Psychiat. **25**:327 (Feb.) 1931.

PROTOCOLS

MONKEY 1.—A portion of field 1 to 3 was excised, as illustrated in the diagram (fig. 3). Post mortem, on microscopic examination, it was found that the white matter had been slightly injured. A small circumscribed portion of field 7 had also been injured, perhaps by a spicule of bone.

Degeneration was seen on the ipsolateral side going in: (1) great masses to field 4, (2) great quantities to fields 7 and 5 and the upper part of field 6 and (3) considerable numbers of fibers to the lower part of field 6.

In addition, a moderate quantity of degenerated fibers was seen running deep in the temporal lobe, with a few fibers rising to the cortex in field 22. The medullary portion of the brain showed a few degenerated fibers farther forward in the frontal lobe than area 6. The lateral thalamic nucleus was definitely affected, and

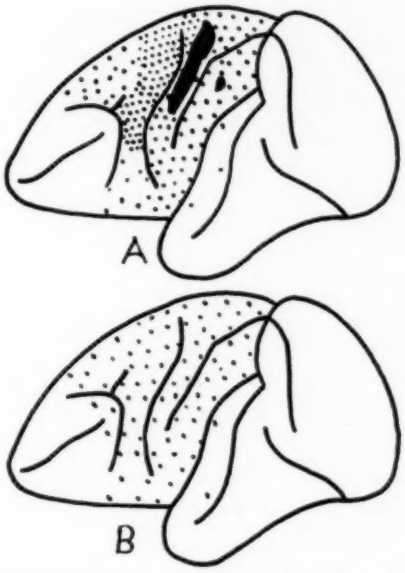

Fig. 3.—Diagrams representing (*A*) left hemisphere and (*B*) right hemisphere of monkey 1.

the internal capsule showed a considerable number of degenerated fibers. The pallidum and putamen showed only the slightest evidence of having been involved. The caudate nucleus and the hypothalamus were clear. Great masses of fibers were seen traversing the corpus callosum. On the heterolateral side, degenerated transcallosal fibers were seen going: (1) in great quantities to fields 1 to 3, 4, 7 and 5, (2) in considerable numbers to the upper part of field 6 and (3) in markedly less numbers to the lower part of field 6, with the same amount to fields 8 *A* and 8 *B*.

There was a little degeneration in the temporal lobe, with occasional fibers rising to the cortex. The remainder of the frontal pole was clear. There was considerable degeneration in the lateral thalamic nucleus and some in the medial thalamic nucleus. The internal capsule also showed considerable degeneration. The pallidum was not affected, but the staining of many slides in this region was poor. The caudate nucleus, the putamen and the hypothalamus were clear.

Monkey 2.—A portion of field 1 to 3 was excised, as illustrated in the diagram (fig. 4). Post mortem, on microscopic examination, it was found that although no additional cortical areas had been injured, again some of the subcortex had been definitely traumatized. Degeneration was seen on the ipsolateral side going in: (1) great quantities to fields 4, 5 and 7 and (2) considerable numbers of fibers to the upper and lower parts of field 6.

In addition, a few fibers came to the surface of field 22, although a far greater number ran deep in the temporal lobe. A moderate number of fibers went to the remainder of the frontal pole, but did not rise to the cortex. The lateral thalamic nucleus showed definite degeneration, and great quantities of degenerated fibers were seen in the internal capsule. The pallidum was definitely but not markedly affected. The caudate nucleus and the hypothalamus were clear, and the putamen was slightly involved. Great quantities of fibers streamed across the corpus cal-

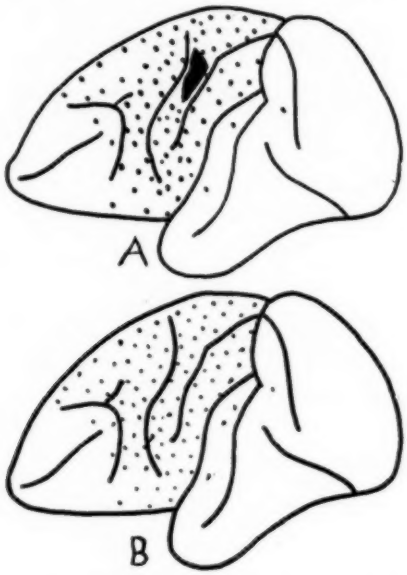

Fig. 4.—Diagrams representing (*A*) left hemisphere and (*B*) right hemisphere of monkey 2.

losum. On the heterolateral side, degenerated transcallosal fibers were seen going in: (1) great quantities to fields 1 to 3, 4, 7 and 5 and (2) considerable numbers to the upper and lower parts of field 6.

A few fibers spread out over the rest of the frontal pole. A fair number of fibers ran deep in the temporal lobe and some spread to the cortex, especially in field 22. The lateral, medial and anterior thalamic nuclei of the thalamus were affected, the first the most markedly. The pallidum and the putamen were definitely but not markedly involved. The caudate nucleus and the hypothalamus were clear. A considerable number of degenerated fibers were noted in the internal capsule.

Monkey 3.—A portion of the cortex of field 6 was excised, as illustrated in the diagram (fig. 5). Post mortem, on microscopic examination, it was found that practically no subcortical tissue had been traumatized. Degeneration was seen

on the ipsolateral side going in: (1) great quantities to the entire frontal pole, but especially to the remaining parts of field 6 and (2) great numbers to fields 1 to 3, 4, 7 and 5.

In addition, many fibers coursed backward deep in the temporal lobe, with slight spreading to the surface of the superior temporal gyrus. The pallidum was practically unaffected. The caudate nucleus, the pallidum and the hypothalamus were clear. Fibers ran down the internal capsule in masses. Many degenerated fibers crossed the corpus callosum. Degeneration was seen on the heterolateral side going: (1) especially to fields 1 to 3, 7, 4 and 5 and (2) in great quantities to field 6. In addition, the degenerated fibers spread over the remainder of the frontal lobe in reduced quantities, and a few came to the cortex of field 22, although many more ran deep in the temporal lobe. Many fibers were noted going to the lateral thalamic nucleus, and many went down the internal capsule. The caudate

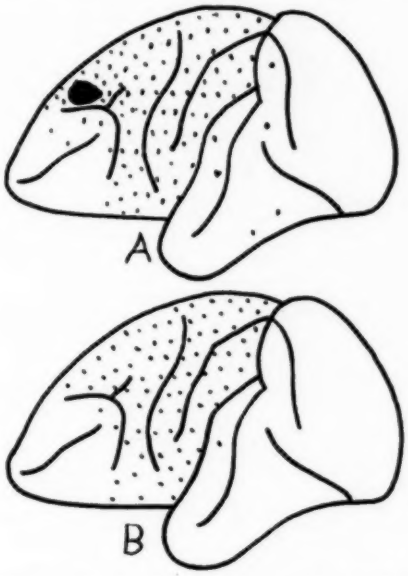

Fig. 5.—Diagrams representing (*A*) left hemisphere and (*B*) right hemisphere of monkey 3.

nucleus and the hypothalamus were clear. The pallidum and the putamen showed only a few degenerated fibers.

MONKEY 4.—A portion of field 6 was excised, as illustrated in the diagram (fig. 6). Post mortem, on microscopic examination, it was found that there had been slight injury to the subjacent medulla. Degeneration was seen going in: (1) great quantities to all the adjacent frontal areas, including 8*a* and 9*c*, (farther forward in the frontal lobe, however, there was little cortical degeneration), (2) masses of degenerated fibers to fields 1 to 3 and 4 and (3) great numbers of degenerated fibers to the cortex of fields 5 and 7.

Many fibers coursed under the temporal cortex, with a few coming to the surface of field 22. A few fibers running under the medial surface of the hemisphere came to the cortex of field 23, but the great majority of the fibers in this area seemed destined for the medial aspect of field 5. The degeneration going to the

thalamus seemed limited to the lateral nucleus. The caudate nucleus and the hypothalamus were clear. The pallidum, especially its medial portion, seemed definitely affected but not markedly so. The putamen contained a few degenerated fibers. Great masses of fibers ran down the internal capsule and many crossed in the corpus callosum. Degeneration was seen on the heterolateral side going in: (1) great masses to field 4, (2) great numbers of fibers to fields 1 to 3, 5 and the upper part of 6 and (3) considerable numbers of fibers, but apparently less than in the other experiments, to field 7 and still less to the lower part of 6.

The remainder of the frontal pole showed a fair amount of subcortical degeneration, with a few fibers going to the cortex, with the exception of field 8, which seemed to be affected as badly as field 6 *B*. A few fibers went to the cortex of field 23. The degeneration to the thalamus again seemed limited to the lateral nucleus. The caudate nucleus and the hypothalamus were clear. The pallidum

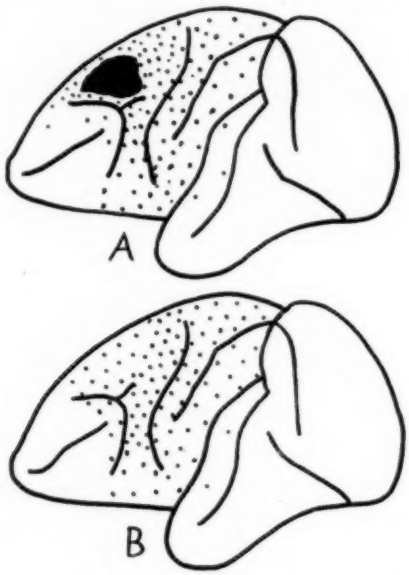

Fig. 6.—Diagrams representing (*A*) left hemisphere and (*B*) right hemisphere of monkey 4.

and the putamen were definitely but only slightly affected. Many degenerated fibers were seen coursing in the internal capsule.

Monkey 5.—A portion of the cortex of fields 7 *a* and 7 *b* was excised as illustrated in the diagram (fig. 7). Post mortem, on microscopic examination, the field was found to be well cut with very little if any subcortical damage. Degeneration was seen going in: (1) heavy strands to fields 1 to 3, 4 and 5 and (2) considerable quantities to the entire cortex of field 6.

The cortex of the remainder of the frontal lobe was free from degeneration, although a few degenerated fibers were noted subcortically. Some degeneration was seen going to the cortex of the superior temporal gyrus and about the same amount to the cortex of field 19 *a*. The lateral thalamus was markedly affected. Many degenerated fibers ran down the internal capsule. The caudate nucleus and the hypothalamus were clear. The pallidum and the putamen were only slightly

involved. A great number of degenerated fibers crossed in the corpus callosum. On the heterolateral side the degenerated transcallosal fibers were seen going in: (1) great quantities to fields 1 to 3, 4, 5 and 7 and (2) slightly lesser quantities to field 6. No degeneration was noted going to the cortex of the remainder of the frontal lobe, and very few degenerated fibers existed there subcortically. The cortex of field 22 was practically clear. The lateral thalamic nucleus showed many degenerated fibers, and a few scattered areas of degeneration were noted in the pallidum and in the putamen. The caudate nucleus and the hypothalamus were clear. The internal capsule was markedly affected.

Additional Factors Common to All Cases.—1. In all brains examined, the occipital subcortex was markedly degenerated on both sides, but in no case did this degeneration come to the surface, except, as mentioned, in monkey 5, in which on the left side some degeneration came to the surface of field 19. This radiation

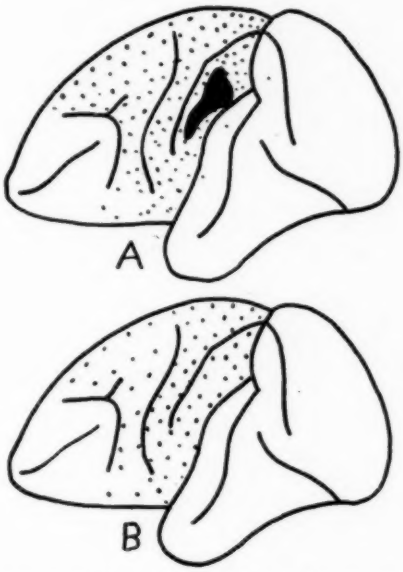

Fig. 7.—Diagrams representing (*A*) left hemisphere and (*B*) right hemisphere of monkey 5.

to the occipital pole seemed to come in all cases mainly by two routes: (*a*) from the injured area or on the other side from the corpus callosum, deep in the temporal lobe, or (*b*) backward through the lateral portions of the corpus callosum itself, on both sides, with many fibers constantly jutting off perpendicular to and through the optic radiation.

2. Although in all the animals the caudatum was carefully examined, in no case was there found the slightest genuine indication of degeneration in this body. The degeneration of the putamen, when noted, was always slight, appeared radially and seemed to be connected with possible aberrant fibers from the internal capsule.

3. In all cases the lateral geniculate body showed many blackened areas. This was puzzling, as I could trace no degeneration to this area. In brains in which a portion of the optic nerve had remained attached and was stained, this too showed blackened Marchi-like degeneration.

COMMENT

Dusser de Barenne's experiments revealed disturbances of sensation over an area that, broadly speaking, contains five well defined fields: 1 to 3, 4, 5, 6 and 7. I worked on only three of these. However, my results for the three seemed to show definitely not only that these cortical areas are intimately and directly connected with each other and with the other two fields on both sides, but that they are in well defined direct anatomic connection with the thalamus on both sides.

A few words are necessary as to the opinions of other authors concerning these anatomic connections. Van Valkenburg [5] cut the corpus callosum in rabbits in an attempt to study the origin and distribution of the fibers crossing from one hemisphere to the other. He could detect positive degeneration only in the cortex of fields 1 to 3, 4, 5 and 7. This observation parallels mine closely, if it is assumed that I should have obtained similar results had I excised the remainder of Dusser de Barenne's fields. The only discrepancy seems to be that van Valkenburg did not include field 6. When one considers that, according to Brodmann,[2] whose charts van Valkenburg [5] used for orientation, field 6 in the rabbit is very small and is overlapped considerably by field 4, and that in his discussion of this field in the rabbit Brodmann stated that an architectonic differentiation of fields 4 and 6 is indicated but that an actual spatial differentiation is possible only with difficulty, I think that one may consider the omission of field 6 by van Valkenburg as of no great importance.

De Vries [6] cut the corpus callosum in mice, but since he was compelled to originate his own cortical architectonic charts for this animal it is difficult to draw any comparison between his work and mine. He concerned himself essentially with the cortical layers affected by the injuries. He found that a diminution in the number of cortical cells invariably occurred in the fifth and sixth layers of the cortex. In my experiments, using the Marchi technic, I found it impossible to judge with any degree of accuracy the exact layer to which the degeneration went. My general impression, however, was that in the fields affected the degeneration usually did not go higher than the fourth layer. I employed the Nissl stain on one brain in which I had excised superficially a portion of field 6, but apparently such a small injury did not lend itself to the degeneration of a sufficiently large number of nerve cells in other areas so that this degeneration could be noted from a slide stained with toluidine blue.

5. van Valkenburg: Brain **36**:119, 1913.

6. deVries: Folia neurobiol. **6**:289, 1912.

Earlier work has shown that the corpus callosum connects the cortices of both sides. Muritow [7] found this to be the case in dogs. Anton and Zingerle [8] stated that considerable radiation from the frontal lobe of one hemisphere attains the distal part of the cortex of the other hemisphere. Probst [9] said the same.

Very few experimental studies seem to be mentioned in the recent literature in relation to corticothalamic connections. Holländer,[10] apparently the last one to concern himself directly with this point, discussed in some detail the corticothalamic tracts in rabbits. However, he did not mention from which fields these fibers originate, nor the

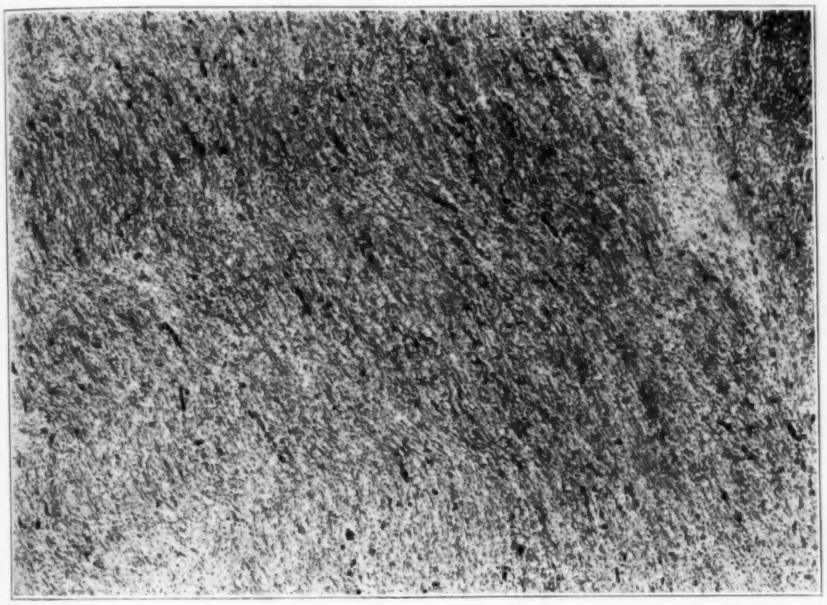

Fig. 8.—Photomicrograph showing degeneration in corpus callosum of monkey 4.

existence or nonexistence of crossed corticothalamic fibers. Tilney and Riley [11] mentioned the short corticothalamic projection fibers, but aside from stating that they conduct impulses from the frontal lobe, supplied no additional anatomic data.

My experiments show that nerve fibers leave the cortex from areas 1 to 3, 6 and 7 and go to the lateral thalamic nuclei of both sides. That

7. Muritow: Neurol. Centralbl. **12**:714, 1893.

8. Anton and Zingerle: Festschrift der Grazer Universität, Graz, Leuschner & Lubensky, 1902, p. 168.

9. Probst: Kais. Akad. der Wissensch. **14**:3, 1905.

10. Holländer: J. de neurol. et de psychiat. **24**:70, 1924.

11. Tilney and Riley: Form and Function of the Nervous System, New York, Paul B. Hoeber, Inc., 1921.

areas 5 and 4 are similarly connected does not appear to be an unreasonable inference. Considering the intimate connection between the fields experimented on with each other and with the remaining sensory areas of Dusser de Barenne, and considering the connections of the areas experimented on with the thalamus, especially its lateral nucleus, and the inferred connection to this nucleus of the other sensory fields, and finally, considering the time-honored relationship of the thalamus to disturbances of sensation, one may consider that a simple anatomic relationship is the basis for Dusser de Barenne's interesting physiologic observations.

A few observations did not entirely fit into this picture. Although one may explain the slight but definite degeneration in field 19 in monkey 5 by the fact that the injured area was not very distant from this field and that therefore some subcortical fibers going to this region were injured, the constant slight damage to the cortex of field 22 on both sides merits attention. The relationship of this field to the other areas I do not know. It is not included in the sensory zone, and in addition it is invariably degenerated far less than the other fields. The only other relationship that comes to my mind is that field 22 is the so-called adversive field of Foerster.[12] The other areas are also either adversive fields or main fields from which epileptic reactions may be elicited. At any rate, fields 6, 7 and 1 to 3 were found to be directly connected by a not overabundant amount of fibers directly with field 22.

In respect to the degeneration observed going to the pallidum, little will be said. This degeneration, it is true, was always present, but it was so slight in amount that it is worthless for the purpose of drawing either positive or negative inferences. Practically the same applies to the putamen.

Okuma [13] found that the frontal cortex is directly connected with the homolateral caudatum. Judging from his illustrations, he injured the frontal lobe very deeply, so that not only the cortex but a great deal of subcortex was badly damaged. In my experiments, the caudatum was surveyed carefully and not once was any genuine Marchi degeneration to be noted therein. Poljak,[14] in his second experiment, found the parietal lobe to be connected with the ipsolateral caudatum. In this case he was working on fields 18 and 19. Withal, his statement that "a system of fine corticofugal fibers descends from the occipital, temporal and frontal regions of the cortex, enter the subcallosal bundle and, turning here partly oral-ward, reach the head of the caudate nucleus," is difficult

12. Foerster: Die Leitungsbahnen des Schmertzgefühls und die chirurgische Behandlung der Schmertzzustände, Berlin, Urban & Schwarzenberg, 1927.

13. Okuma: Okayama-Igakkai-Zasshi **42**:2806, 1929.

14. Poljak: J. Comp. Anat. **44**:197, 1927.

to reconcile with my observations, unless the frontal corticocaudate fibers originate from frontal areas farther forward than field 6.

My observations in regard to the capsula interna appeared interesting and possibly important. The presence of degeneration in the capsula interna on the homolateral side was to be expected, but the presence of definite and considerable degeneration in the capsula interna on the opposite side seems worthy of comment. A review of the recent experimental literature gives little information in regard to this point.

At a meeting of the German Neurological Society, in 1926, Mingazzini [15] stated that Niessl von Mayendorf had noted that after cortical softening on one side the callosal fibers were damaged and

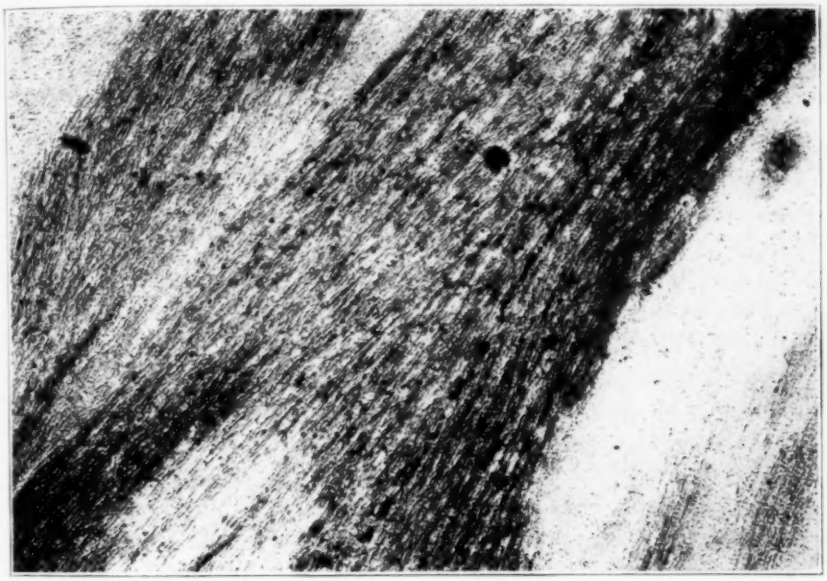

Fig. 9.—Photomicrograph showing degeneration in internal capsule of monkey 3.

extended to the internal capsule of the other side. From serial sections in a case of hemiplegia, Mingazzini concluded that a considerable portion of callosal fibers coming from the right hemisphere bend above the left caudate and help to form the left internal capsule. He called this the "gekreutzte Balken-Stabkrantz" bundle, but seemed to think that it originates in the pallidum. In the discussion that followed, it was mentioned that Foville, Hammond and Wernicke previously had noted this crossed callosal internal capsule tract, but that Oscar Vogt had denied its existence. Muratow explicitly denied the presence of any crossed

15. Mingazzini: Zentralbl. f. d. ges. Neurol. u. Psychiat. **44**:784, 1926.

callosal internal capsule fibers after his experimental work (animal?). Since the Marchi technic is fallible, I think it not amiss here to insert an unretouched photomicrograph of a portion of the right internal capsule in monkey 3 (fig. 9). The Marchi degeneration is here mainly in fibers cut obliquely, but one fiber is cut horizontally. Considering the difficulty of photographing Marchi sections, I do not think that there is any doubt that this photograph demonstrates genuine Marchi degeneration.

The degeneration of the capsula interna does not occur in circumscribed bands, but tends to spread out rather diffusely. However, similarly to the degeneration in the corpus callosum, brains operated on in frontal areas showed the greatest concentration of degeneration in the corpus callosum and internal capsule rather far forward, while the brain operated on in area 7 showed the height of degeneration considerably farther back. In the last case, in the capsula interna the degeneration was greatest just behind the knee.

The black spots that I usually found in the corpus geniculatum externa I decided to consider as artefacts, because not only were they not perfectly characteristic of Marchi degeneration, but the opticus notedly gives trouble in Marchi studies; in addition, the degeneration-like products here were totally unconnected spatially with any coming from above.

CONCLUSIONS

In the brain of Cercopithecus, cortical areas 6, 7 and 1 to 3 have been found to be in intimate direct connection with each other and also with areas 4 and 5 homolaterally and heterolaterally.

Areas 6, 7 and 1 to 3 have been found to be in direct connection with the lateral thalamic nuclei of both sides.

By analogy, areas 4 and 5 may have similar connections, and, if so, a simple anatomic relationship can be invoked to explain the presence of bilateral disturbances of sensation when one of these areas is experimentally poisoned.

Fibers from the cortex of areas 6, 7 and 1 to 3 travel not only down the capsula interna of the same side but, via the corpus callosum, down the capsula interna of the opposite side.

The cortex of areas 6, 7 and 1 to 3 sends no direct fibers to the caudate nucleus or to the hypothalamus, and few if any to the pallidum and to the putamen.

ARE PHYSIOLOGIC DISTURBANCES RELATED TO THE ACUTE PSYCHOTIC PROCESS IN THE MENTALLY ILL?

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ZURICH, SWITZERLAND

There are in the literature many isolated reports of functional derangement of some of the physiologic processes of the body in cases of acute psychoses. In this paper I shall attempt to demonstrate the constancy of these manifestations in certain types of cases, and to show that with a remission of the acute psychologic disturbances these derangements also approach normal standards.

In 1902, Reiman [1] reported the presence of glycosuria in the mentally ill, especially in cases of depression. He quoted Legrand du Saulle as finding that there was an intermittent glycosuria in cases of dementia paralytica and that this state was present only when the dementia paralytica was accompanied by depression. Folin, Dennis and Smellie [2] reported finding sugar in the urine of psychotic patients. Lorenz,[3] in studying the blood sugar tolerance of mental patients, reported higher curves for the manic-depressive psychoses of depressed type. Henry and Mangam [4] corroborated this observation in the affective psychoses and in cases of "acute dementia praecox." Of special interest in this connection is the work of Bogen,[5] who, in addition to a definite increase in the blood sugar in thirteen of eighteen cases of affective psychoses, demonstrated a marked increase of epinephrine circulating in the blood stream in three cases of depression and in one manic case; nine patients showed an increase as compared with normal controls.

This work was done at the Pennsylvania Hospital, Department for Mental and Nervous Diseases, Philadelphia.

1. Reiman, Emil: Ztschr. f. Heilk. **23**:1, 1902.

2. Folin, O.; Dennis, W., and Smellie, W. G.: Some Observations on Emotional Glycosuria in Man, J. Biol. Chem. **17**:519, 1914.

3. Lorenz, W. F.: Sugar Tolerance in Dementia Praecox and Other Mental Disorders, Arch. Neurol. & Psychiat. **8**:184 (Aug.) 1922.

4. Henry, George W., and Mangam, Elizabeth: Blood in Personality Disorders, Arch. Neurol. & Psychiat. **13**:743 (June) 1925.

5. Bogen, D.: Biological Studies of the Blood in the Affective Psychoses, Rev. psychiat., neurol. & reflexol. (Leningrad) **4**:78, 1929; abstr., Am. J. Psychiat. **9**:1161, 1930.

In the case of the gastro-intestinal tract, Farr and Lueders [6] demonstrated from normal to increased gastric secretion in manic patients, but failed to show any increase in this direction in depressions. By means of roentgen examinations, Henry [7] demonstrated changes from a normal condition to hypertonicity and hypermotility of the digestive tract in the manic phases of the affective psychoses. Furthermore, a difference obtains between normal controls and persons with affective psychoses in their vegetative response to the intravenous injection of ephedrine, as well as a difference in their galvanic responsiveness. Thus, in either phase of an affective psychosis, Palmer [8] obtained in the fasting patient, in response to the intravenous injection of a fixed dose of ephedrine, a rather typical blood sugar curve which revealed a rapid drop away from the fasting level as compared with the results obtained in normal controls. Westburgh,[9] in psychogalvanic studies, found good evidence that pronounced cases of mania and depression give little or no deflection, but show a marked increase in galvanic responsiveness as the patient improves.

The frequency with which, as well as the constancy of the type of the psychosis in which, these various dysfunctions have been demonstrated leaves little doubt that these various observations represent more than a mere factor of coincidence. Nevertheless, may not these findings represent the normal of any physiologic function for any patient? Especially may this be the case with the gastro-intestinal functions. It is known that in the latter, as in many of the other systems, the physiologic functions show individual variations, all compatible with health. Without knowing what is normal for a given patient, one cannot demonstrate the abnormal. In only a few instances is it known that the reported findings represented an abnormal or pathologic state. Thus, Schulze [10] has already stated: "The intensity of the glycosuria was an index of the depression, for with resolution of the glycosuria, there was a parallel resolution of the depression." Raphael, Ferguson and Searle,[11] in making a serial study of the blood sugar of a depressed patient, found a gradual change in the curve in the direction of normal as the patient improved, until with recovery it had almost reached the usually accepted

6. Farr, Clifford B., and Lueders, Charles W.: Gastric Secretory Functions in the Psychoses, Arch. Neurol. & Psychiat. **10**:548 (Nov.) 1923.

7. Henry, George W.: Some Observations of Gastro-Intestinal Conditions Associated with Mental Diseases, Am. J. Psychiat. **3**:695, 1924.

8. Palmer, Harold D.: Personal communications to the author (to be reported).

9. Westburgh, Edward M.: Psychogalvanic Studies on Affective Variations in the Mentally Diseased, Arch. Neurol. & Psychiat. **22**:719 (Oct.) 1929.

10. Schulze: Verhandl. d. Gesellsch. deutsch. Naturf. u. Aerzte **80**:538, 1908.

11. Raphael, Theophile; Ferguson, William G., and Searle, Olive M.: Long Section Blood Sugar Tolerance Study in a Case of Depression, Arch. Neurol. & Psychiat. **19**:120 (Jan.) 1928.

physiologic standard. As already mentioned, Westburgh found an increased galvanic responsiveness as the patient's affective psychosis improved.[11a]

MATERIAL

In order to study further some of these functions, gastric analyses were made in various types of psychoses, and sugar tolerance tests in cases presenting chiefly an affective symptom complex. In a few cases both tests were performed on the same patient within an interval of one day, especially in those with the latter type of syndrome, thus allowing a comparison of the results of both tests in the same patient under almost the same conditions. Furthermore, in this type of case, a limited number of patients could be subjected to both tests at intervals and followed through to recovery, thus obtaining a simultaneous check of both dysfunctions. In the accompanying tables the tabulated results show that the quantitative reaction to both tests in the same patient was almost parallel, and with improvement the results approached simultaneously the normal standard.

(*a*) *Gastric Analyses.*—For the purpose of the gastric analyses the following technic was used:[12]

> Three fasting specimens of gastric juice were taken at five minute intervals, followed by the introduction of 1 Gm. of Liebig's beef extract diluted in 50 cc. of water through the tube already in place. Continuous extraction was then begun, separating the secretion into ten, fifteen, fifteen, and fifteen minute specimens and titrating each separately. The use of beef extracts as a stimulant results in a higher percentage of acid concentration. Since in this work the acid concentration rather than the amount secreted was used as the index, 60 per cent of free hydrochloric acid was considered the maximal normal concentration.

In table 1 are given the results of fifty-four separate analyses in nine different types of subjects, these various subjects having been selected to obtain some standard for comparison. Of this series, all those having an acid concentration of over 60 per cent, twenty-six in number or 48 per cent, had acute psychoses or a predominant affective element in the clinical picture. Of this series of cases, two of depression and one of neurosis showed achlorhydria. Table 2 gives the results of serial tests on patients who showed definite improvement or who recovered.

11a. Since this manuscript went to the publishers, Zondek (Zondek, H., and Bier, A.: Brom im Blute bei Manisch-depressivem Irresein, I., Klin. Wchnschr. **11**:633 [April] 1932) reported the results of his investigations of the bromide content in twenty-three cases of manic-depressive psychosis. In either phase of the psychosis he demonstrated a reduction to what was definitely below the normal content (from 0.8 to 1 mg. of bromide per hundred cubic centimeters of blood, a norm which is not affected by climatic, seasonal or nutritional variations or by the menstrual cycle of the female); with improvement or recovery this lowering of the bromide content of the blood again returned to the average normal standard.

12. Farr, Clifford B.: Personal communications to the author.

(*b*) *Sugar Tolerance.*—For this purpose the Jensen-Hagedorn method was used. A specimen of blood was taken with the subject in the fasting state. The patient was given 1.75 Gm. of dextrose per kilogram of body weight, diluted in 500 cc. of water. A specimen of blood

TABLE 1.—*Results of Fifty-Four Gastric Analyses in Nine Patients* *

	Types									
Acid concentration	1	2	3	4	5	6	7	8	9	10
Achlorhydria	..	1	4	..	2	..	..	..	..	7
Below 50%	3	..	..	1	1	1	4	6	..	16
50–60%	1	1	..	..	1	..	..	..	2	5
60–90%	..	2	..	..	3	7	..	1	3	16
Over 90%	..	..	..	..	4	5	..	..	1	10

* Types: 1, normal; 2, psychoneurosis; 3, pernicious anemia; 4, dementia paralytica; 5, depressions; 6, manic-depressive psychosis of manic type; 7, chronic hypomania; 8, dementia praecox, and 9, acute schizophrenic reaction.

TABLE 2.—*Results of Serial Tests in Cases of Improvement or Recovery*

Case	Maximum Free Hydrochloric Acid, per Cent * (1)	(2)	(3)	Diagnosis
1	81	..	47	Manic-depressive psychosis, manic type
WBT	61	..	28	Manic-depressive psychosis, manic type
FHR	108	77	52	Manic-depressive psychosis, manic type
JND	98	74	38	Manic-depressive psychosis, depressive type
RTB	102	85	75	Manic-depressive psychosis, manic type
JGA	82	62	..	Acute schizophrenic reaction
WMG	68	..	42	Manic-depressive psychosis, manic type
FOT	0	7	..	Schizophrenia with depression
WGP	0	..	26	Psychosis with depression
PLL	0	..	21	Manic-depressive psychosis, depressive type

* The three columns under the headings of (1) (2) and (3) indicate the grade of improvement in the direction of recovery.

TABLE 3.—*Results of Tests for Sugar Tolerance without the Dextrose Meal* *

Sugar Tolerance Curve					Fasting Curve					Clinical Picture
0.090	0.172	0.212	0.210	0.211	0.106	0.106	0.109	0.107	0.104	Manic-depressive, agitated depression
0.095	0.161	0.301	0.170	0.174	0.107	0.099	0.106	0.112	0.113	Manic-depressive, dementia paralytica
0.114	0.206	0.232	0.208	0.151	0.099	0.097	0.099	0.105	0.098	Manic-depressive, depression

* Readings are expressed in milligrams per hundred cubic centimeters of blood.

was then taken after one-half, one, one and a half and two hours. The same technic was used throughout. Chart 1 shows the results of twenty-five such tests graphically represented, all the cases in this series being of the affective psychotic type.

In order to determine whether emotions created as a result of subjecting the patient to the test might perhaps be a responsible factor, the same

series of blood specimens was taken from three patients of the same group without giving them the dextrose meal. The results are shown in table 3.

In table 4 the initial and final results of serial tests for sugar tolerance are given. The initial curve represents the results during the psychotic state, while the final curve represents the improved or recovered state. The results of tests between the initial and final tests are omitted. The cases bear the same initials as those in table 2, to facilitate comparison of quantitative results of both tests in the same patient.

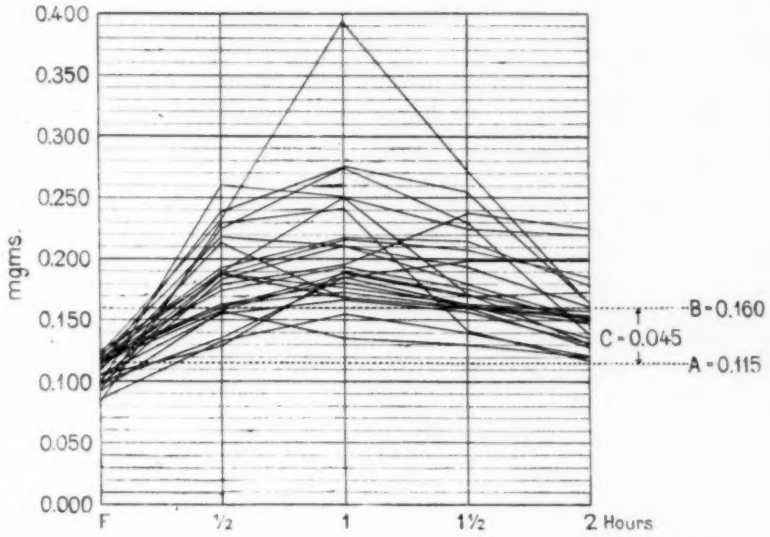

Chart 1.—Results of tests for sugar tolerance in twenty-five cases (seven, manic-depressive psychosis of manic type; thirteen, manic-depressive psychosis of depressive type; five, acute schizophrenic reaction). *A*, mean fasting level. *B*, mean level for two hours. *C*, difference of 0.45 mg. per hundred cubic centimeters, mean delay for the group.

TABLE 4.—*Initial and Final Results of Tests for Sugar Tolerance* *

Case	Psychotic State			Final Test			Clinical Picture
JND	0.114	0.180	0.196	0.112	0.179	0.165	Manic-depressive, depression
	0.238	0.225		0.142	0.136		
WMG	0.113	0.239	0.276	0.110	0.115	0.137	Manic-depressive, manic
	0.255	0.164		0.120	0.108		
WIV	0.108	0.162	0.181	0.081	0.161	0.217	Manic-depressive, depression
	0.216	0.224		0.172	0.137		
GIN	0.105	0.156	0.167	0.098	0.104	0.156	Manic-depressive, manic
	0.157	0.150		0.173	0.122		
WOR	0.118	0.190	0.250	0.104	0.165	0.190	Acute schizophrenic reaction
	0.225	0.220		0.174	0.163		

* Readings are expressed in milligrams per hundred cubic centimeters of blood.

COMMENT

The results here reported are those of gastric analyses made in part, and sugar tolerance tests made exclusively, on mentally ill patients who presented a predominant affective element in their clinical picture. In most of the cases the psychotic process was of rather acute onset. Of the fifty-four patients subjected to a gastric analysis, twenty-six showed an acid concentration of over 60 per cent, and three showed a total achlorhydria. Whenever possible, serial follow-up analyses were made on the same patient; these revealed that with improvement these gastric secretory dysfunctions approached normal standards (table 2). Further, an analysis of the graph in chart 1 shows that in this type of case the sugar tolerance curve showed at the end of two hours a delay in its return to the fasting level, a fact often reported in the literature. However, with improvement or recovery from the psychotic episode, this physiologic anomaly also improved or returned to normal.

In normal subjects, experimental and clinical evidence has shown that any emotional stimulus producing a transient affective state inhibits the biologic reflexes, such as gastric and salivary secretion. The immediate effect of the two tests reported and such apprehension as they may have produced seemed to have no influence on the results, as is shown by their constancy on repetition, though for the purpose of the test the patient occasionally required restraint by means of a pack. Table 3 shows further that the fasting blood sugar curve was not materially influenced by the technic of the test. Westburgh,[13] in psychogalvanic studies, had already made the same observation; he found that only with recovery from the psychosis were results approximating those in normal controls obtained. From these various sources of evidence it may then be assumed that the physiopathologic mechanisms responsible are the expression of a process that is rather stable; it seems little affected by the emotions produced by the average daily environmental stimuli, and such resulting affective states and concomitant reaction as they may exert on the vegetative nervous system. All evidence seems to point in the direction that only with resolution of the affective psychotic process do these observed functional disturbances return to an accepted normal state.

The observations here reported together with those reported in the literature seem to be of some importance because they seem to refute the argument often advanced, namely, that these disturbed physiologic functions are the result of emotional states produced by environmental stimuli acting on the patient. What seems more probable is that the acute psychosis represents a process, the psychologic and physiologic

13. Westburgh, Edward M.: Psychogalvanic Studies of Normal and of Abnormal Subjects, Arch. Neurol. & Psychiat. **22**:453 (Sept.) 1929.

symptoms being respectively components of the same syndrome. The patient still seems to react to stimuli of the environment to some degree, but this deepseated process seems little affected by them. Graphically, this might be represented as in chart 2.

Another point of interest is: Why did three of the cases of this series show a complete achlorhydria, which likewise improved with recovery from the psychosis? The exact dynamics underlying the process in these affective psychoses, which also seems to be responsible for these physiologic disturbances, still remains to be demonstrated. All that seems evident in these experimental investigations is that the patient showed either an achlorhydria or an increased gastric acidity, and in the case of the tests of sugar tolerance a delay in the return to the fasting level. However, Pavlov,[14] in his studies of conditioned reflexes, had already found that in certain dogs in which he had produced a "pathologic state or a neurosis," as he termed it, identical stimuli, when applied under identical conditions, might in one instance produce a salivary inhibition and in

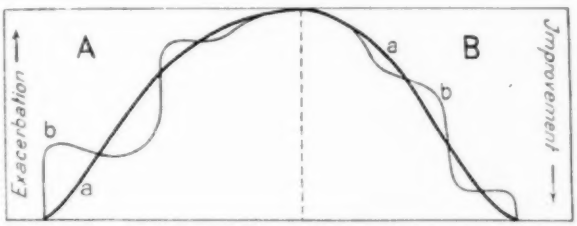

Chart 2.—*a*, the process of abnormal physiologic responses of the biologic reflexes during the acute psychotic stage. *b*, minor responses of the autonomic nervous system to stimuli of the environment. These stimuli have apparently no effect on the "process" illustrated by curve *a*. *A*, as the psychosis reaches the acute stage, the process *a* predominates; the reaction to environmental stimuli, *b*, decreases. *B*, as the psychosis improves in the direction of recovery, the process *a* gradually disappears; the vegetative responses to environmental stimuli *b* approach those of normal standards.

another an excitation, and that the process predominating at any given time persisted. Inhibition or excitation of salivary secretion in the last analysis is an expression of autonomic function. Some such analogous disturbance in the integrated action of the autonomic system governing these other physiologic functions probably also accompanies these pathologic states in man.

SUMMARY AND CONCLUSIONS

1. A brief review of the literature reveals that functional derangements of various of the physiologic processes have been demonstrated repeatedly in patients suffering from an acute affective psychosis.

14. Pavlov, I. P.: Conditioned Reflexes, London, Humphrey Milford, 1929.

2. The results of gastric analyses and blood sugar tolerance tests in this same type of case herein reported have further demonstrated the existence of such disturbances during the acute stage of the psychosis. Furthermore, it has been shown that with improvement or clearing up of the psychotic process these functional disturbances again approached a normal state, indicating that for any given patient these observations represented a pathologic state.

3. Emotional states produced by immediate environmental stimuli, including the technic of the test, had no apparent effect on the results. These dysfunctions appear rather stable, and together with the psychologic symptoms probably represent the expression of the same underlying process. In speaking of improvement hitherto, the psychologic disturbances have been taken into consideration, but paralleling these the physiologic disturbances also approach accepted normal standards. What usually happens in this type of patient is that he either improves slowly, rapidly recovers completely or passes over into a chronic state. From a psychiatric standpoint the clinical picture in the chronic cases then changes; hallucinations or delusions, or both, may persist or the patient deteriorates. When the patient presents this state of the psychosis, these physiologic disturbances can no longer be demonstrated.

Psychiatrische Universitätsklinik.

Clinical Notes

BLOOD PRESSURE OBSERVATIONS IN TUMORS OF THE BRAIN

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For some time I have thought that patients with tumors of the brain have a blood pressure that is perhaps lower than is usually found in a person of that particular age, so much so, in fact, that in my studies of patients who present themselves showing evidence of chronic cerebral impairment I have come to be biased against the diagnosis of tumor of the brain in the presence of arterial hypertension. In order to determine whether I am justified in this attitude of bias against the diagnosis of tumor in patients with arterial hypertension this review has been undertaken and 100 cases from my files of verified tumors of the brain have been studied. No effort has been made to select the cases; they are consecutive cases, except that two groups have not been included in the study. The two groups omitted are the pituitary tumors and those in patients under 20 years of age. The reason for excluding from consideration these two groups seemed to be logical, for I wished, in the case of patients with pituitary tumors, to avoid a criticism that might justly have been made—that is, that the well known metabolic disturbance so often found in these cases might have been a factor in the lowered blood pressure. For the purpose of this paper, however, this group of cases would materially have affected the averages, as they uniformly presented a low pressure; in fact the lowest readings were encountered in this group.

In this study, no effort was made to obtain the lowest blood pressure noted in the records. In the vast majority of cases the blood pressure recorded at the time when the history was taken and the physical examination was made is the one on which the study is based. In a few instances, in which this observation was not made at the time of admission, it was necessary to use the blood pressure reading which the anesthetist made on the patient's entry to the anesthesia room, but in no case was a reading used that was made while the patient was under an anesthetic. In the former case, owing to the excitement incident to admission to the hospital, or in the latter case, preliminary to an operation, it might be argued that these are not the ideal times for obtaining data to support my contention, but I wished to be as consistent as possible in the presentation of the material.

The second decade of life is characterized by wide variations in blood pressure, and, according to reliable insurance statistics, there is as much average increase in blood pressure from the ages of 10 to 20 years as there is in the next forty years. Various investigators have shown wider variations in averages of blood pressure between the ages of 12 and 16 years than are found in any other similar period of time. Blood pressure also increases in children with changes in height and weight.

Read at a meeting of the Society of Neurologic Surgeons, Richmond, Va., June 5, 1931.

From the Neurosurgical Clinic of Dr. C. C. Coleman, Hospital Division, Medical College of Virginia, Richmond, Va.

These facts seem to indicate that blood pressure tends to become more "established" after the age of 20 and to justify the exclusion of the first two decades from consideration in this analysis. However, if the cases of tumor in patients under 20 years of age were included, the blood pressure averages for the group analyzed would not be raised.

Present knowledge regarding averages of blood pressure comes largely from the insurance companies, and to the medical directors of these companies we are indebted for the rapid increase in knowledge on this subject. Insurance companies soon realized the importance of studies of blood pressure and began to insist that blood pressures be recorded according to a specified technic in the case of every person applying for life insurance. From their records it is learned that both systolic and diastolic pressures increase with age; the pulse pressure increases slightly with age, but varies considerably with persons in good health. Blood pressure varies with build, increasing with the percentage over and descreasing with the percentage under average weight. It is about 3 mm. lower in women than in men in the younger ages, but about the same from middle age on.

The "American Standard" [1] hereafter referred to is taken as a basis for comparison with the blood pressure in our cases. This standard was obtained from averages of 250,000 Americans accepted for life insurance.

Search through the various systems of medicine, as well as textbooks and the literature in general has revealed that little consideration has been given to the relation between intracranial tension as found in tumors of the brain and systemic arterial pressure, except by some authors who insist that the blood pressure is not elevated or, indeed, is of no particular significance.

In 1811, Ravina, an Italian experimenter, inserted a glass window in the skull of a laboratory animal in an attempt to demonstrate pulsations of the brain within the closed cranial cavity. Cushing [2] was the first in this country to take up the study of similar phenomena for the purpose of observing the pial circulation and the cortex of the brain in the living animal during an increase in intracranial pressure. He wished to determine whether the smaller blood vessels of the brain were dilated from venous stasis during cerebral compression or whether a condition of capillary anemia was brought about by such a state, and the bearing of these and other phenomena on the practical handling of states of cerebral compression as found in tumors of the brain. These experiments carried out with the aid of ingenious devices enabled him to watch the effects on the pial vessels in conditions of controlled cerebral compression and at the same time to record the systemic arterial pressure. His observations have been amply confirmed by Wolff and Forbes,[3] and Wolff and Blumgart,[4] who have gone a step further in their studies on cerebral circulation. The contribution from this experimental work is best

1. Hunter, Arthur. Blood Pressure, What Affects It? New York, 1914. (Mr. Hunter is the chief actuary of the New York Life Insurance Company.)

2. Cushing, Harvey: Concerning a Definite Regulatory Mechanism of the Vaso Motor Centre Which Controls Blood Pressure During Cerebral Compression, Bull. Johns Hopkins Hosp. **12**:290, 1901; The Mutter Lecture for 1901, Some Experimental and Clinical Observation Concerning States of Increased Intracranial Tension, Am. J. M. Sc. **124**:375, 1902; The Cameron Prize Lectures: Intracranial Physiology and Surgery. The Third Circulation, New York, Oxford University Press, 1926.

3. Wolff, H. G., and Forbes, H. S.: The Cerebral Circulation, Arch. Neurol. & Psychiat. **20**:1035 (Nov.) 1928.

4. Wolff, Harold G., and Blumgart, Herman L.: Cerebral Circulation, Arch. Neurol. & Psychiat. **21**:795 (April) 1929.

summarized by quoting Cushing's own words: "An increase in intracranial tension occasions a rise in blood pressure which tends to find a level slightly above that of the pressure exerted against the medulla. It is thus seen that there exists a regulatory mechanism on the part of the vasomotor center which, with great accuracy, enables the blood pressure to remain at a point just sufficient to prevent the persistence of an anemic condition of the bulb demonstrating that a rise is a conservative act and not one such as is consequent upon a mere reflex sensory irritation." This experimental observation holds true in acute compression from any cause whenever the pressure reaches a level sufficiently high to affect the medulla, but does not obtain in cases of cerebral tumors in which the compression is more gradual and extends over a period of weeks and months. In cases of chronic pressure, such as that due to tumor, it may be that some other regulatory mechanism becomes operative and maintains a normal or lower arterial pressure. An acute compression may arise from hemorrhage into or edema about a tumor with an abrupt rise of the systolic blood pressure. Frazier [5] has expressed himself as follows: "Inasmuch as the blood pressure is not disturbed in brain tumors to any appreciable degree in any case and not at all in most cases, to my mind this clearly eliminates the arterial pressure as a factor." Sachs,[6] in a recent monograph, stated that for the past nineteen years in his clinic, where routine observations on blood pressure have been made, no changes of note have been observed, although Riddoch reported having seen a rise in blood pressure in case of tumor of the brain. I have not seen expressions from any other clinics on this subject. On the other hand, Reyes [7] stated that in his cases blood pressure was of interest only in two instances: One patient, a woman, aged 60, with chronic interstitial nephritis and general arteriosclerosis, had a systolic blood pressure of 90. She had a tumor of the temporal lobe. Another woman, aged 45, with a tumor of the frontal lobe, had a blood pressure of 80 systolic and 45 diastolic. He recorded blood pressure readings in only six cases, however.

An analysis of the 100 cases studied from this clinic follows: Ninety-seven patients were white and 3 colored; 62 were males and 38 were females; 71 were recorded as having choked disks, while 29 had normal disks. Only 3 showed a positive Wassermann reaction: A Negro, aged 40, had a gumma of the motor cortex with symptoms of four months' duration; a white man, aged 29, had a gumma of the corpus callosum with symptoms of six weeks' duration, and the third patient had a glioma. This man, aged 45, had had symptoms for fourteen years; the blood pressure was 114 systolic and 72 diastolic, and a glioma of the temporal lobe was found at operation.

The shortest period of symptoms, four days, was found in a man, aged 33, whose blood pressure was 120 systolic and 80 diastolic. Seven patients had a systolic blood pressure above the upper limit for normal of the "American Standard," which is 135 systolic and 89 diastolic. The other 93 had blood pressures below this figure. The lowest blood pressure recorded in this series was found in a man, aged 45, whose pressure was 90 systolic and 60 diastolic, and in whom an intraventricular tumor was found after seven months of symptoms; he had a choked disk. A similar pressure was found in a white woman, aged 52, whose

5. Frazier, C. H.: The Cerebrospinal Fluid and Its Relation to Brain Tumors, New York M. J. **99**:1275 (June) 1914.

6. Sachs, E.: The Diagnosis and Treatment of Brain Tumors, St. Louis, C. V. Mosby Company, 1931.

7. Reyes, Carmelo: Tumors of the Brain Among Filipinos, Arch. Neurol. & Psychiat. **22**:1217 (Dec.) 1929.

symptoms dated back two years and from whom an endothelioma of the frontal lobe was removed; her disks were normal. Another blood pressure below 100 systolic was found in a man, aged 41, who had been having headaches for twelve months, and from whom an endothelioma of the parietal lobe was removed; his disks were normal. A low blood pressure was found about as often in patients with normal disks as in those with choked disks, so that the mere fact of increased intracranial tension did not seem to have any direct bearing on blood pressure. In this clinic, lumbar punctures are seldom performed in cases in which tumor of the brain is suspected. Obviously, if there is evidence of increased intracranial tension in the eyegrounds, the procedure is not indicated and is generally contraindicated.

Some of the lowest blood pressures were found in patients whose eyegrounds were perfectly normal. As an illustration of this, recently an endothelioma, weighing 105 Gm., was removed from the motor cortex of a woman, aged 51, who

TABLE 1.—*Cases with High Blood Pressure*

Age	Duration of Symptoms	Disks	Blood Pressure	Kind and Location of Tumor
40	6 weeks	Choked	142/ 90	Glioma temporal lobe
46	6 weeks	Choked	150/ 90	Glioma frontal
49	3 months	Choked	150/ 80	Glioma frontal
41	6 months	Normal	140/ 90	Endothelioma motor cortex
54	18 months	Choked	190/120	Endothelioma motor cortex
56	7 weeks	Normal	176/ 90	Endothelioma parietal lobe
56	10 weeks	Normal	140/ 90	Endothelioma parietal lobe

TABLE 2.—*Classification as to Location of Tumors*

Location	Number of Cases	Average Age	Average Blood Pressure	"American Standard"
Frontal	25	40	115/71	126/84
Parietal	9	43	123/71	127/84
Temporal	25	43	114/73	127/84
Motor cortex	17	43	116/73	127/84
Cerebellum	8	32	114/76	123/82
Acoustic neuroma	11	39	118/74	126/84
Miscellaneous	5	36	110/67	124/83

had been having jacksonian attacks for nine years. Spinal puncture was not done, and there was no clinical evidence of increased pressure, as the patient had never complained of headaches, nausea, etc. In seventeen other cases, in which the systolic pressure was 100 or below, the ages of the patients were: 29, 30, 32, 35, 35, 39, 40 44, 44, 45, 47, 48, 48, 51, 51, 52 and 55.

Fifty-two patients had a systolic pressure under 120, while the pressure in 16 others was an even 120. In other words, of the 100 studied 68 patients, all above the age of 20, had a systolic pressure below the "American Standard" for the age of 20.

Each of the 7 patients with tumor in the series who had a high blood pressure presented definite evidence of cardiovascular renal disease. An analysis of these cases is given in table 1; all occurred in white men. Eight other patients in the series showed similar evidence of definite cardiovascular renal disease, and in no case was the blood pressure above normal as is usual in such cases.

In table 2 the cases are arranged according to the location of the tumor. It will be seen that in each group the averages for blood pressure are below those of the corresponding "American Standard."

In table 3 are shown the blood pressures arranged according to age. All of the seven patients with an elevated blood pressure had at the same time a complicating disease (cardiovascular renal), which is in itself often associated with hypertension. If these cases are omitted from consideration, the averages for the fourth decade would be reduced to 113 systolic and 73 diastolic and the fifth to 114 systolic and 75 diastolic, as three were in the former and four in the latter age groups.

SUMMARY AND CONCLUSIONS

One hundred verified cases of tumor of the brain are presented, with a tabulation of the blood pressure readings. Pituitary tumors and tumors in persons under 20 years of age have been excluded. All of the 7 patients with an elevation of blood pressure showed evidence of cardiovascular-renal disease. The remaining 93 patients showed a blood pressure that was definitely lower than the blood pressures of normal people of a corresponding age, as given by the American Standard.

TABLE 3.—*Classification as to Age Groups*

Age	Number of Cases	Average Blood Pressure	"American Standard"
20 to 30	19	119/64	122/81
30 to 40	21	109/62	125/84
40 to 50	40	115/73	129/85
50 to 60	18	124/79	133/88
60 to 70	2	124/70	137/90

A study of this series appears to justify the opinion that an elevation of blood pressure above the normal is infrequent in uncomplicated tumor of the brain; if the blood pressure is elevated above the normal in such cases it is usually due to some accompanying disease which commonly causes an increase of vascular tension.

A SIMPLE AND EFFECTIVE METHOD OF REENFORCING THE KNEE JERK

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The knee jerk occupies an important place as a routine diagnostic procedure. It is a reflex that is elicited in the majority of normal people with ease, but in a small and disturbing minority with more or less difficulty. In most cases it is the patient's inability voluntarily to relax the quadriceps muscle group that interferes with the proper response. It is self-evident that the knee jerk cannot take place unless the quadriceps group is at least partially relaxed.

Many tricks have been devised with the object of "reenforcing" the knee jerk by diverting the patient's mind from his quadriceps, thus permitting it to relax.

From the Thorndike Memorial Laboratory, Second and Fourth Medical Services (Harvard) of the Boston City Hospital and the Department of Medicine of the Harvard Medical School.

The method most commonly employed is the so-called "Jendrassik's method" [1] in which the patient hooks both hands together, pulling them against one another, and looks up toward the ceiling, thereby shifting the focus of his attention and relaxing the muscles of the leg. In Laufenauer's method [1] the patient grasps the arm of the examiner and gives it a squeeze just as the patellar tendon is being struck. Other methods advocated are having the patient do small sums in arithmetic or repeat the Lord's prayer,[2] pricking the patient with a small needle or shining a bright light in his eye.[3] All of these procedures depend entirely on distraction of the patient's attention. This may be difficult or impossible if he is acutely aware of what is being attempted. A method that reflexly diminishes the tension of the quadriceps muscles in addition to diverting the attention would appear to produce the most favorable conditions for eliciting the response. In accordance with this idea, the following procedure has been used to reenforce the knee jerk.

The patient, who is in the supine position with the knee slightly flexed, is asked to press against the bed with the back of the heel, i. e., to contract the hamstrings. The leg thus supports itself so that the examiner can lay one hand on the quadriceps to detect the slightest contraction. The reflex relaxation of the quadriceps, resulting from the voluntary contraction of the antagonist muscle group, causes exaggeration of the knee jerk in normal persons and brings out "latent" knee jerks in a number of cases in which the classic methods of reenforcement are unavailing. This test also has the advantage of simplicity and can be carried out with sick patients in bed. Over a period of several years it has proved satisfactory as a routine clinical procedure.

A search of modern textbooks of neurology reveals no method that utilizes the principle of reflex inhibition of the antagonist muscle group for reenforcing the knee jerk. Going back to original sources, however, one finds that Jendrassik himself recognized and utilized this principle. Speaking of cases in which it is difficult to elicit the knee jerk because of inability to relax the quadriceps, he said: "In such a case it is well for the patient to cross his knees and to press down with the thigh which is uppermost in order that by contraction of the muscles in antagonism to the quadriceps the innervation of the latter will be hindered." [4]

In a physiologic study of the knee jerk three years later, Weir Mitchell [5] pointed out clearly that voluntary contraction of the hamstring group of muscles greatly exaggerates the knee jerk.

It seems strange that after nearly fifty years the well known principle of reflex inhibition and its utilization for the reenforcement of the knee jerk have not found universal application.

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1. Quoted from Stewart, J. P.: Diagnosis of Nervous Diseases, ed. 5, London, Edward Arnold, 1920, p. 321.

2. Jelliffe, S. E., and White, W. A.: Diseases of the Nervous System, New York, Lea & Febiger, 1915, p. 52.

3. Oppenheim, H.: Text-Book of Nervous Diseases; English Translation, London, T. N. Foulis, 1911, vol. 1, p. 7.

4. Jendrassik, Ernst: Beiträge zur Lehre von den Sehnenreflexen, Deutsches Arch. f. klin. Med. **33**:177, 1883.

5. Mitchell, S. Weir.; and Lewis, M. J.: Physiological Studies of the Knee-Jerk, and of the Reactions of Muscles under Mechanical and Other Excitants, M. News **48**:169, 1886.

SPECIAL ARTICLE

TREATMENT OF EPIDEMIC ENCEPHALITIS

A REVIEW OF THE WORK OF THE MATHESON COMMISSION

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The treatment of epidemic encephalitis is purely empiric. The causative agent has not been definitely proved. Of course, determining this might not be of much help in therapy. This is certainly true in the therapy of infantile paralysis, which is known through experimental transmission to be due to a specific filtrable virus. Moreover, the finding of a specific method of treatment need not wait on the determination of the cause. It was known that quinine was specific in malaria and mercury in syphilis long before the plasmodium of malaria or Spirochaeta pallida was discovered. Certainly the effects of epidemic encephalitis are so terrible that finding a cure for this disease is one of the most challenging problems that confronts the medical profession.

The course of epidemic encephalitis is such that an estimate of the therapeutic value of any agent is extremely difficult to make. The mortality of the acute stage of the disease has varied greatly in different outbreaks, and it is impossible to say whether or not it has ever been modified by the many methods of treatment that have been used. The mortality in the series of more than 450 acute cases observed by the meningitis division of the New York Department of Health,[1] in which the patients were treated only with lumbar puncture, was about 25 per cent. This is about the same percentage as that in other series of cases in which the patients were treated in various ways.

After the patient has recovered from the acute stage, months or even years must elapse before it will be known whether he is really cured or whether the infectious agent has only been lying dormant. In certain instances the patient passes directly from the acute into the chronic stage of the disease.

Read by title before the Association for Research in Nervous and Mental Disease, Dec. 28, 1931.

1. Neal, J. B.; Jackson, H. W., and Appelbaum, E.: Study of Four Hundred and Fifty Cases of Epidemic Encephalitis, Am. J. M. Sc. **170**:708, 1925.

The methods used in treating the various stages of epidemic encephalitis include most of the drugs listed in the pharmacopeia, all kinds of vaccines and serums and all known methods of physical therapy and psychotherapy. All the methods of treatment in both the acute and the chronic stages are reviewed in the report of the Matheson Commission [2] published in 1929, and in the second report, published in 1932.[3]

It would be useless and tiresome to attempt to review the innumerable methods of therapy that have been used. Many of them were apparently tried for no reason whatever. In other instances drugs or other means of therapy were employed for symptoms that may arise in the course of many diseases and therefore have no particular relation to encephalitis. However, many measures have been used in an effort to destroy the infectious agent and to alleviate the symptoms characteristic of encephalitis and the various complications sometimes arising directly due to this disease.

METHODS OF TREATMENT

The more important of these measures may be listed as follows:

I. *Methods for the Destruction of the Infecting Agent.*—These are:

A. Chemicals:
1. Acriflavine and other dyes
2. Salicylates
3. Iodine preparations
4. Colloidal metals
5. Arsenicals, including arsphenamine preparations
6. Mercury derivatives, including mercurochrome-220 soluble

B. Production of febrile reactions:
1. Numerous nonspecific proteins
2. "Fixation abscess"
3. Malarial inoculations
4. African recurrent fever
5. Fever-producing baths

C. Serums:
1. Convalescent serum
2. Rosenow's encephalitis antistreptococcic serum
3. Gay's herpes hyperimmune rabbit serum

D. Vaccines:
1. Levaditi's herpes recovered rabbit brain vaccine
2. Gay's herpes hyperimmune rabbit brain vaccine
3. Rosenow's vaccine for encephalitis
4. Stewart's Pfeiffer vaccine

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2. Matheson Commission: Epidemic Encephalitis, New York, Columbia University Press, 1929.

3. Matheson Commission: Epidemic Encephalitis, New York, Columbia University Press, 1932.

Since it is now generally believed that the chronic stage of the disease is caused by the continued activity of the infecting agent, measures aimed at the destruction of this agent would be applicable at all stages. It is unnecessary to state that most of these types of treatment have yielded results that have been unconvincing.

The use of convalescent serum seems particularly unjustified in view of the fact that so many patients fail to produce sufficient antibodies to check the course of the disease in themselves. Moreover, if it is assumed that the disease is caused by a neurotropic strain of the herpes virus, it is important to note that Gay and Holden [4] have shown that these patients are actually more deficient than the average in antibodies against the herpes virus. It would be a difficult task to select donors whose recovery was really assured.

II. *Methods for Modifying the Course of the Disease by Reducing Intracranial Pressure.*—These consist in:

1. Hypertonic dextrose solution intravenously
2. Hypertonic iodide solution intravenously
3. Lumbar puncture

Beneficial results have been obtained by all these methods in certain cases. The hypertonic dextrose solution certainly is valuable in building up depleted patients and improving the action of the heart as well as in decreasing intracranial pressure. The action of the iodides is not so definite.

III. *Methods for the Control of Symptoms.*—These include:

A. Drugs:

1. Duboisine, scopolamine, stramonium and atropine
2. Bulbocapnine
3. Ephedrine sulphate
4. Sedatives, hypnotics and analgesics, as phenobarbital, bromides, amytal, chloral hydrate, etc.

B. Endocrine therapy

The various symptoms for which these drugs are used are too well known to require discussion.

Scopolamine and allied preparations often bring temporary relief in tremor, rigidity and other manifestations of the parkinsonian syndrome. It has been our experience that patients taking these drugs over a long period have frequently increased the dosage to a point where toxic effects were obtained. It sometimes happens that cumulative effects result even when the dose is small. It has often been difficult to per-

4. Gay, F. P., and Holden, M.: The Herpes Encephalitis Problem, J. Infect. Dis. **45**:415, 1929.

suade the patient to reduce the dose, and sudden withdrawal of the drug is dangerous. That these drugs are habit-forming does not seem to be generally appreciated. We strongly deprecate the routine use of these drugs at clinics where patients are not under close medical supervision.

Atropine preparations, particularly a belladonna preparation, have been useful in our experience in controlling sialorrhea, and they have not seemed to be habit-forming.

The use of bulbocapnine has been largely discontinued because of its toxic effects.

Ephedrine sulphate has been recommended for narcolepsy, but it has not been used in a sufficient number of cases to draw definite conclusions as to its value.

Oculogyric crises have been treated with a measure of success by the atropine group, especially scopolamine or genoscopolamine, by the intravenous injection of a 10 per cent solution of calcium chloride, by epinephrine, by chloral hydrate and by paraldehyde.

IV. *Methods for Building up General Resistance, Health and Morale.*—These consist in:

A. General hygienic measures, as diet, rest and proper elimination

B. Removal of foci of infection

C. Tonics:

1. Sodium cacodylate
2. Iron preparations
3. Strychnia
4. Other tonics as indicated

D. Physical therapy:

1. Hydrotherapy
2. Electrotherapy, including diathermy
3. Roentgen treatment
4. Massage
5. Graduated exercise and reeducation of muscles

E. Occupational therapy

F. Psychotherapy

General hygienic measures are of great importance at all stages of the disease, and especially during the acute stage. A prolonged period of complete rest is essential even in seemingly mild cases.

While we do not hold with those who believe that encephalitis is caused by toxins elaborated by focal infections, we do think that patients with encephalitis are adversely affected by these toxins and that it is therefore especially important that these focal infections be eradicated.

Sodium cacodylate is highly recommended, especially in the subacute and chronic stages of the disease. It is given in large doses, either subcutaneously or intravenously.

Strychnia has been used with success in asthenic patients.

The value and methods of the more common forms of physical therapy are too well known to require comment. It may be noted that the improvement occasionally following roentgen treatment of the head was stated by von Economo [5] to be due probably to the vasodilator effect of the irradiation and the subsequent hyperemia of the atrophic basal ganglia. A similar effect may be produced by diathermy.

It is most important to combat by every possible means the discouragement that patients suffering from chronic epidemic encephalitis are bound to feel. To this end patients should be urged to interest themselves in suitable forms of occupation, in games and in other methods of entertainment. Fatigue must always be avoided, but exercise within the limits of their capacity is essential.

Every effort should be made to encourage a spirit of optimism and courage, for the will to recover, or the lack of it, plays no small part in the progress in most cases. This is a form of psychotherapy. In certain instances patients suffering from physical symptoms in a large measure due to mental conflicts have been improved by psychoanalysis or hypnosis.

Comment.—The multiplicity of remedies used in treating patients with epidemic encephalitis connotes the lack of agreement in regard to their efficacy. Except for certain of the general measures listed under group IV and a few drugs used for symptomatic treatment, there is the widest divergence in the treatment of the disease as carried out by different physicians of wide experience. Unfortunately, many physicians who are treating large numbers of patients suffering from encephalitis have not published the methods that they have used.

It may be of interest to contrast the treatment advocated by Stern [6] and von Economo,[5] who have recently published monographs on encephalitis.

Stern stated that in the acute stage of the disease the best remedy, the most specific and the most prolonged in its effect, is convalescent serum; it is successful not only in saving life, but also in preventing the development of the chronic stage. Intramuscular injections were as effective as intraspinal. It is stated that 70 per cent of patients treated with convalescent serum are able to carry on their work after a period of more than three years following the acute illness. In a number of his cases the serum treatment was followed by other therapeutic measures, as acriflavine hydrochloride, arsenic preparations or injections of milk.

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5. von Economo, C.: Die Encephalitis lethargica, ihre Nachkrankheiten und ihre Behandlung, Berlin, Urban and Schwarzenberg, 1929.

6. Stern, Felix: Die epidemische Encephalitis, ed. 2, Berlin, Julius Springer, 1928.

The chemical preparations that Stern has found most useful in the acute stage are acriflavine hydrochloride, the collargol preparations and sodium salicylate. He has not had satisfactory results with Pregl's solution or other iodine preparations. He does not advocate lumbar puncture as a therapeutic measure in the acute stage.

In the so-called "pseudoneurasthenic" stage he used convalescent serum with varying results. He also recommended acriflavine hydrochloride and arsenic, especially sodium cacodylate, in this stage.

In the chronic stage he recommended atropine or other belladonna preparations, such as scopolamine, and sodium cacodylate in large doses, either alone or more often in combination with these alkaloids.

Von Economo wrote that the medical treatment of choice for acute cases is the intravenous administration of large doses of iodine; all other remedies are only adjuvants. He used Pregl's solution or a 10 per cent aqueous solution of sodium iodide in doses up to 100 cc. If for any reason the iodine preparation cannot be given intravenously, intramuscular injections of some form of iodized oil may be used, but with less effect, or the iodides may be given internally with still less benefit.

Simultaneously with the iodine treatment, von Economo administered an autolysate of staphylococci and Bacillus prodigiosus, subcutaneously, intramuscularly or intravenously, in increasing doses to produce fever. At the same time methenamine was given by mouth or intravenously.

This combination—iodine, the autolysate of staphylococci and Bacillus prodigiosus and methenamine—the author called "classic" therapy. He recommended lumbar puncture in patients with increased spinal fluid pressure and also subcutaneous injections of solution of pituitary for symptoms of increased cerebral pressure.

If the iodine treatment is not successful, other remedies may be tried: convalescent serum, the value of which he questioned on account of the chronicity of the disease, acriflavine hydrochloride, silver preparations—as a colloidal silver preparation or dispargen—calcium chloride, eucupin or iso-acetylhydrocupreine (vuzin). Von Economo was not convinced of the value of salicylates, given either intramuscularly or intravenously.

He stated that the autolysate of staphylococci and Bacillus prodigiosus is the best remedy for the isolated discomforts (as neuralgia, headaches, disturbances of sleep, twitchings, etc.) that persist for some time after the acute stage or which arise later. These are the most easily combated of the sequelae. The most obstinate are parkinsonism and the pseudopsychopathic sequelae.

The author treated every patient with parkinsonism by the methods outlined for the acute stage. He also recommended sodium cacodylate, intravenously, in large doses. The treatment is repeated yearly and sometimes gives good results.

These seemingly divergent methods of treatment as regards the use of convalescent serum by Stern and iodine preparations and the autolysate of staphylococci and Bacillus prodigiosus by von Economo may perhaps be reconciled on the theory that both constitute forms of shock therapy. Moreover, since neither author used controls, it is impossible to draw definite conclusions in regard to the value of either method.

MATERIAL AND RESULTS

Since the summer of 1929, the Matheson Commission has been making a clinical study of a large number of cases of epidemic encephalitis at the Neurological Institute in New York. While most of these patients have been in the chronic stage of the disease, a special effort has been made to include all acute cases available.

It was planned to have all patients brought to the Neurological Institute for at least a week for a complete neurologic, laboratory and roentgen examination. A similar examination was made on groups of patients in other hospitals that cooperated with us. Without the splendid cooperation of the entire staff of the Neurological Institute this work would have been impossible. The Kings Park State Hospital, Manhattan State Hospital, United States Veterans' Hospital No. 81 and Montefiore Hospital aided in the study and treatment of groups of patients. Private physicians also contributed a number of patients for our study.

A total of 584 patients has been collected from these different sources. In a certain number the diagnosis was later found to be incorrect. A few patients have died, and others have not continued under treatment. In other instances, the patients have not been treated sufficiently to be included at this time. We are making a preliminary report on 370 patients.

For carrying out treatment, clinics are held twice weekly at the Neurological Institute for ambulant patients. Nurses visit the homes of patients who are unable to travel. In some instances the treatment is administered under our direction by local physicians or nurses to patients living at a distance. A certain number of patients remain under the care of their private physicians, who administer the treatment and report to us in regard to progress. The majority of the patients, however, return to us for periodic reexaminations.

In planning the study of treatment, the Matheson Commission was confronted with two main theories in regard to the etiology of epidemic encephalitis: that it might be a form of the herpes virus, as claimed by Levaditi and others, or that it might be a neurotropic form of the Streptococcus viridans, as claimed by Rosenow and Evans and Freeman.

It was therefore planned to carry out treatment by measures that might be specific for these two etiologic agents, namely, Rosenow's encephalitis antistreptococcus serum and vaccine and Levaditi's rabbit brain vaccine. Levaditi's vaccine was prepared by injecting his neurotropic herpes virus C, originally obtained from a case of encephalitis, intracerebrally into a group of rabbits, using such a dose that a part of the rabbits died and the remainder recovered after showing symptoms of encephalitis. The brains of the rabbits that recovered were emulsified, and after sterility tests were used as a vaccine. The vaccine was first prepared for us in Dr. Gay's laboratory from a strain sent to him by Levaditi.

In a short time, however, the strain lost its virulence so that none of the rabbits thus given injections died. After some experiments, Dr. Gay devised a method of immunizing rabbits with a dermotropic strain of herpes virus. These rabbits were then tested for immunity by the repeated intracerebral injection of multiple lethal doses of a strain of herpes virus isolated by Perdrau from a case of encephalitis. The brains of rabbits found to be immune were used to make a vaccine that Dr. Gay has designated as the hyperimmune rabbit brain vaccine. These rabbits were also bled, and the serum was used in the treatment of a small number of patients with acute encephalitis. The details of the preparation of Gay's hyperimmune vaccine and serum have not been published, and this brief account is given through his courtesy and with his approval.

Dr. Rosenow has been generous in supplying us with his vaccine and serum for the group of patients treated by this method.

The number of patient treated in the acute stage is so small that no definite conclusion can be drawn. In all, twenty-six have received treatment. Of these, fifteen received Levaditi's vaccine or Gay's hyperimmune vaccine; seven, Gay's hyperimmune rabbit serum; four, Rosenow's serum. In some instances the patients are still under treatment, and in none of them has sufficient time elapsed to determine to what degree the chronic stage will develop. Five of the patients have died, a mortality slightly less than 20 per cent. In so small a group this means nothing, and it does not seem worth while to analyze the results in the few patients treated by each of these means of therapy.

In dealing with patients in the chronic stage of the disease, it seemed logical to assume that if either of these theories of etiology was correct an effective therapy might result from active immunization. Accordingly, we used Rosenow's vaccine and Levaditi's rabbit brain vaccine, which were soon supplanted by Gay's hyperimmune rabbit brain vaccine. At the same time, respective control groups were formed; one group of patients was treated with hemolytic streptococcus vaccine prepared by Gay; a second received normal rabbit brain vaccine, and a third, at Kings Park State Hospital, received only routine treatment.

Rosenow's vaccine was given at weekly intervals, hypodermically, in doses beginning with 0.1 cc. and increasing by 0.1 cc. to 3 cc. With most patients a period of rest of from six weeks to two months was instituted every six months.

The hyperimmune rabbit brain vaccine and the normal rabbit brain vaccine were given intramuscularly at weekly intervals in courses of 66 cc., three doses of 2 cc. each and fifteen doses of 4 cc. each. This dosage was adopted arbitrarily. After a period of rest, usually of two months, the course was repeated. Some patients are taking the fourth course of treatment. It may be stated that no one who was administering the vaccine or making the reexaminations knew until later which was the hyperimmune vaccine and which was the control.

The patients under treatment were reexamined, as a rule from every three to six months, and more often if there was any marked change. At each treatment brief notes were made in regard to the patient's condition.

While it would have been desirable from a scientific standpoint for each patient to continue with the method of treatment on which he was started, this was at times impossible. In a few instances a change was necessary on account of severe reactions. When patients remained stationary or steadily became worse during a considerable period of treatment, a change was instituted. This was necessary in order to retain the patients.

In treating the patients who were immediately under our control we have avoided prescribing drugs of the scopolamine group and have endeavored to persuade those patients who were already taking them to diminish the dose or to eliminate them altogether. At times it has been necessary to give preparations of belladonna for sialorrhea or profuse sweating. Sedatives, analgesics and tonics have been prescribed when necessary. A special effort has been made to have foci of infection removed or treated. Dr. Edmonde D. Neer showed deep interest and cooperated in working with these patients.

Our staff has endeavored to encourage patients to take regular exercise and to interest themselves in occupations, games and amusements. On account of the financial condition of most of our patients it has not been possible, however, to make use of the various forms of physical therapy that would have been desirable.

The estimation of improvement in cases of chronic epidemic encephalitis is extremely difficult because of the marked irregularity of the natural course of the disease. We realize that observation over a period of only two years is entirely inadequate to judge definitely of the result of any method of therapy and that our statements in regard to the condition of the patients are purely tentative. We have observed that most patients show a temporary improvement with any method of treatment.

In drawing conclusions in regard to improvement when reexaminations are made, the statements of the patients themselves are largely discounted. The symptoms that are especially evaluated are rigidity, tremor, gait, posture, facial expression, speech, difficulty in swallowing, sialorrhea, oculogyric crises, disturbances of sleep and other symptoms less easy to weigh, such as fatigability, mental depression, emotional instability and disorders in behavior. We have tried to be particularly conservative in classing patients as improved and have disregarded slight changes for the better in a single symptom. In several patients there has been evidence of marked improvement in many symptoms, but the extension of tremor to a part not heretofore involved has indicated that the disease was progressing.

The accompanying table shows the present evaluation of 352 patients who are under active treatment and 18 untreated controls, who have been recently reexamined. In this table, C indicates Levaditi's rabbit brain vaccine; A and X, Gay's hyperimmune rabbit brain vaccine; B, normal rabbit brain vaccine, and streptococcus H, Gay's control hemolytic streptococcus vaccine.

Active Cases; Data Available Oct. 1, 1931 *

	Total	Slightly Improved	Improved	Much Improved	Total Improved	Percentage Improved	Stationary	Worse	Total Unimproved	Percentage Unimproved
C, X and A										
Continuous	101	50	10	3	63	62+	28	10	38	37+
Transfers	14	..	..	..	..	....	6	8	14	....
Total	115	50	10	3	63	54+	34	18	52	45+
Institutions	39	..	11	..	11	....	..	..	28	....
Total	154	50	21	3	74	48+	..	..	80	51+
(One course, 66 cc. to more than 3 courses)										
B										
Continuous	22	7	1	..	8	36+	11	3	14	63+
Transfers	12	..	..	..	..	....	9	3	12	....
Total	34	7	1	..	8	23+	20	6	26	76+
Institutions	11	..	..	..	..	....	9	2	11	....
Total	45	7	1	..	8	17+	29	8	37	82+
(One course, 66 cc. to 2 courses)										
Rosenow's Vaccine										
Continuous	81	35	8	1	44	54+	26	11	37	45+
Transfers	39	..	..	..	..	....	25	14	39	....
Total	120	35	8	1	44	36+	51	25	76	63+
Institutions	15	..	..	..	..	....	15	..	15	....
Total	135	35	8	1	44	32+	66	25	91	67+
(Treated 4 mos. to 1 yr. 11 mos.; 70 more than 1 yr.)										
Streptococcus H										
Continuous	6	..	3	..	3	50	2	1	3	50
Institutions	12	..	..	..	..	....	..	..	12	....
Total	18	..	3	..	3	16+	..	..	15	83+
(Treated 7 to 9 mos.)										
Untreated Controls										
Kings Park State Hospital	18	..	..	..	..	....	4	14	18	100
Total number of patients, 370										

* This table shows the results of treatment of patients with chronic cases with the different vaccines. It is based on the treatment under which the patient was started, and there is no duplication.

The heading "Continuous" is applied to groups of patients who have remained under one method of treatment. The heading "Transfers" is applied to groups of patients in whom treatment was begun with the therapeutic agent under which they are listed, but who were subsequently changed to some other method of treatment. There are no duplications. It may be noted that a smaller proportion of transfers was necessary in the group started with the hyperimmune rabbit brain vaccine than in any other group.

The heading "Institutions" indicates patients studied and treated at the Kings Park State Hospital, Manhattan State Hospital, United States Veterans' Hospital No. 81 and Montefiore Hospital. These patients showed less improvement than the patients who were not institutionalized. In some of these patients the disease was very far advanced, but in the group of patients who are under our care there are many in the advanced stage of the disease.

We realize that the arrangement of groups is not ideal. It would perhaps have been desirable to have more controls. However, our combined control groups include eighty-five patients either untreated or treated by obviously nonspecific vaccines.

It is impossible to draw definite conclusions from the groups treated by Rosenow's vaccine and by Gay's hyperimmune rabbit brain vaccine. The improvement of 32 per cent in the group treated by Rosenow's vaccine cannot be passed over lightly. This vaccine may conceivably act in any one of three ways. If the disease is due to the neurotropic Streptococcus viridans, it may have a specific action. On the other hand, it may act favorably on any focal infections, which are present in so many of these patients, thereby improving the general health of the patient and lessening a possible toxic effect from the focal infections of the central nervous system. Finally, it may act simply as a foreign protein.

The percentage of improvement in the group receiving C and Gay's hyperimmune rabbit brain vaccine is decidedly higher than that in any other group. It is 48 per cent, as compared with 17 per cent in the group receiving normal rabbit brain. It is obvious, therefore, that the improvement from the hyperimmune rabbit brain vaccine cannot be due to a nonspecific protein reaction. Is it possible that it is due to a specific action on the infecting virus? The answer to this lies in the study of these patients over a long period and especially in the study of the progress of patients treated in the acute stage of the disease in whom, if its action is specific, the virus may be killed before irreparable damage to the brain tissue has been done.

We must emphasize again that we are drawing no conclusions from the studies thus far made. We are keeping constantly in mind that the course in a case of epidemic encephalitis cannot be predicted. Remarkable improvement may take place with or without treatment, or a patient may grow progressively worse and then reach a stage at which he remains stationary for years. It is only after the careful study of large numbers of patients treated in different stages of the disease over a long period of time that any definite conclusions can be reached.

The results thus far, admittedly inconclusive, seem to warrant and even necessitate the continuation of the study of the effects of treatment in this large group of patients.

45 Gramercy Park.

Abstracts from Current Literature

RESEARCHES ON THE PATHOLOGY OF CERTAIN ENCEPHALOMYELITIDES DUE TO VIRUSES. G. MARINESCO and S. DRAGANESCO, Rev. neurol. **1**:1 (Jan.) 1932.

In his report before the International Neurologic Conference at Bern, Marinesco devoted the first part to a study of herpes, rabies, poliomyelitis and zoster, with a few words on typhus. In the second part, he took up in brief the demyelinizing diseases and their pathogenesis.

The findings are based on clinical and pathologic investigation, and particularly on animal experimentation.

1. *Herpes.*—Herpes encephalitis is rare in man, but is easily produced in animals by corneal inoculation. In its centripetal migration the virus produces inflammatory reactions in the nerves, semilunar ganglion and pons, spreading thence into the surrounding nerve tissues and involving the meninges and perivascular spaces and the septums, with marked proliferation of the microglia. Inoculation in other areas produces lesions in ascending fashion; for instance, in cases in which the retina is inoculated the inflammation progresses along the optic nerve. The injection of herpetic virus into the sciatic nerve produces primary lesions in the spinal cord. Section of the nerve prevents the migration of the virus, although it can arrive by the vascular route. It is not yet decided whether the virus travels along the axis cylinders or by the perineural lymphatics, but lymphadenitis is usually present and strong compression of the nerve without section does not prevent the development. The diffusion of the virus in the neuraxis is principally by the perivascular spaces and spinal fluid, less by the intramedullary nerve fibers.

2. *Rabies.*—Lesions in the central nervous system predominate on the side of the bite, especially in the spinal and sympathetic ganglia connected with the bitten area. The nerves often show severe changes, and the spinal ganglia may show necroses that are at times suggestive of zoster. The later progress of the disease takes it principally to the midbrain, where the substantia nigra and the walls of the third ventricle are severely affected. The medulla oblongata is likewise severely diseased, although less destruction takes place here. Injection of virus into nerves is much more effective if a sensory nerve is used than in a pure motor nerve like the hypoglossal, indicating that the virus travels by the nerve fibers themselves; these fibers can be shown to undergo marked alterations. Immunity to rabies may be transmitted through the placenta, although no lesions are found in the brain. The relation of the Negri bodies to the rabies is of importance. These probably contain the virus, but when the evolution of the disease is rapid these corpuscles are not formed.

3. *Poliomyelitis.*—Poliomyelitic virus follows the route of the axis cylinders rather than the blood stream or fluid, and the primary lesions are often found in the nervous system in the location where these fibers originate or terminate. It is uncertain, however, whether the portal of entry is shown by the development of localized palsies, since the portal is supposed to be the nasopharynx and yet the paralysis often begins in the lowermost segments. The microglial reaction in poliomyelitis is intense and diffuse, rather than perivascular, and the cerebral peduncles develop an appearance like that in epidemic encephalitis. Differences are particularly the absence of inflammatory lesions in the lenticular nucleus in poliomyelitis and the actual destruction of ventral horn cells which does not take place in epidemic encephalitis. Inflammation of the spinal ganglia is not uncommon in poliomyelitis, but the peripheral nerves do not show infiltrating lesions. Hyperplasia of lymphatic structures is common.

4. *Zoster.*—The eruption contains the virus of the disease and does not represent merely a trophic disorder due to inflammation of the ganglion. The large balloon

cells are seen to contain intranuclear inclusions; there are inflammatory reactions about the finer branches of the nerve, and the virus follows along the nerve fibers after penetrating into them. These nerve filaments often show destruction of myelin, with release of fat. "The same general factors, such as the least resistance, p_H and oxidation reduction in the tissues (hodogenesis), bring about the transmission and migration of zona virus as herpes virus."

5. *The Demyelinizing Myelitides.*—The division of inflammations of the nervous system into inflammatory lipolytic and lipotrophic does not give a true conception of the difference, because all the demyelinizing diseases are characterized by disintegration of the myelin, which is phagocytosed by the microglia. The disintegration is due to digestive hydrolytic ferments, as in other cases of degenerating nerves. Different tissues possess different hydrogen ion concentrations. The skin, for instance, varies from p_H 3.5 superficially to 7.4 or 7.6 in the base. "The increase of hydrogen ion concentration brings about slowing of the phenomena of oxidation and retention in the tissues of products of incomplete oxidation and even acids. Increase in hydroxyl ions has a contrary effect in increasing oxidation. Investigation of the biochemical structure of nerve fibers and nerve centers has shown a diastatic system represented in nerve fibers by iron, primary catalyst in the myelin and lipase which is ordinarily inactive, whereas in the nerve cells the diastatic system is represented by iron and an oxydase attached to the colloidal masses of the cytoplasm. Rabies virus in iso-electric determinations has a p_H between 5.8 and 7.4, possesses a negative charge and tends toward a positive pole. The results of injection of an emulsion containing virus which tends toward the positive pole are different from those of a virus which tends toward the negative pole. This change in the reaction of the medium of herpes virus brings about a change in its virulence. This property is probably possessed by all neurotropic viruses. On the other hand, the oxydases of nerve cells are destroyed when virus attacks gray matter and activates hydrolytic enzymes where the potential is altered."

FREEMAN, Washington, D. C.

BEHAVIOR IN ITS RELATION TO THE DEVELOPMENT OF THE BRAIN. F. TILNEY and L. S. KUBIE, Bull. Neurol. Inst., New York **1**:159 (June) 1931.

This study is one of the projects of the research program of the Neurological Institute which attempts to correlate behavior and adaptive reactions with development of the brain and cerebral structure. It is a lengthy article of some eighty pages and contains only the first portion of the outlined work, i. e., the maturing process in the domestic cat. Concurrent studies on (*a*) the development of the brain and (*b*) the development of behavior are to follow.

The genesis of behavior is considered as a comprehensive biologic process having a definite structural basis in the mechanisms by which the reactions of life are made possible. All mammals, including man, are distinguished by a cerebral cortex (neocortex). The degree of development of this structure varies, as does also the capacity for adjustment; these find their highest attainment in man. The authors have been studying the correlation of mammalian behavior and brain structure for several years. The present report outlines the method of study and summarizes the findings up to the present time.

The work is based on the assumption that all structures of the body must attain adequate differentiation to be capable of specialized reactions, and that such specialization can be best determined in the nerve tissue through the study of development of cell processes and myelinization. The opossum, rat, guinea-pig, pig, cat and man were selected for study because of the availability of material and the facility for controlled observation before as well as after birth. The pigs are included to disclose specialization characteristic of the hoofed animals. The desirability of including the infrahuman primates is recognized, but lack of material made this impossible.

Development of behavior is studied by observations and records begun immediately after birth and continued until maturity. Schedules showing successive

addition of definitely specialized behavior reactions are used to indicate phases for the structural study of the brain. The neocortex receives chief attention, as it is predominant in the adjustive reactions of man and to a large extent in all mammals, but other structures in the endbrain and interbrain are also included in the study. The following methods are used: (1) organogenetic studies by means of the Born reconstruction method, (2) histogenetic studies by means of cellular and fiber stains and (3) myelinogenetic studies by means of the Weigert myelin stain.

The literature on the studies of processes in the expansion of the cerebral cortex is reviewed. The developmental processes in the endbrain of the domestic cat are given, with detailed descriptions of: (*a*) the three layer stage recapitulating conditions in the ichthyopsid brain; (*b*) the appearance of the cortical zone and the four-layer stage, recapitulating reptilian conditions, and (*c*) the earliest surface distinction between the paleocortex and the olfactory bulb. The material is well illustrated with sketches and plates. The development of the tract beds in the endbrain was also studied. The earliest development in the fiber tracts was approximately coincident with the inception of the cortical zone. Reconstructions were made to show the hemisphere and interbrain as a whole on the right side and the tract beds alone on the left. The earliest tract beds appear in the forebrain of the 13 mm. stage and include (1) the lateral olfactory tract, (2) the optic tract and (3) the thalamocortical tract. The lateral olfactory tract bed arises in the frontal region, from which the olfactory bulb subsequently differentiates. The tract beds show a decided extension in the 17 mm. stage, coincidental with the clearer definition of the paleocortex. A fourth tract bed, originating near the frontal pole and extending back to the cortical tract, appears in the 20 mm. stage. Another appears in the 31 mm. stage, and at the 40 mm. stage the metathalamic structures can be differentiated. In the 75 mm. stage the fibers forming the corpus callosum have appeared.

The chronologic order in the development of tract beds related to the neocortex gives priority to the afferent projection system functionally connected with general body sense. The afferent projection system of the special senses appears at later periods. The interhemispheral association fibers of the neocortex are the latest to appear in prenatal life. There was no demonstrable evidence of development in either the long or short interhemispheral association fibers. The authors conclude that the functional evolution of the neocortex, which represents the highest specializations in behavior, depends in the cat on: (1) projection of the senses on specialized neocortical areas, with general body sense preceding the special senses, (2) the bilateral association of these senses in the two hemispheres, (3) intimate associations and elaborations within each type of sense as well as interassociations between all the senses and (4) the afferent projection of sensory associations into the somatic effector activities of the animal's behavior. It is thought that this formula for the functional evolution in the neocortex may, with certain modifications, be applied to all mammals. KUBITSCHEK, St. Louis.

CHRONIC SUBDURAL HEMATOMA. SIMPLE DRAINAGE AS A METHOD OF TREATMENT: REPORT OF EIGHT CASES. HOWARD W. FLEMING and O. W. JONES, JR., Surg., Gynec. & Obst. **54**:81 (Jan.) 1932.

The authors advocate a minor surgical procedure in the treatment of chronic subdural hematoma in place of the more radical and accepted methods for complete removal of the sac and its contents. The method is described as follows: "To make, under local anaesthesia, four trephine openings in the fronto-parietal and parieto-occipital regions of either side. The incisions are so fashioned and the openings so placed that they may be incorporated in an osteoplastic flap at a subsequent date if this is necessary. Small openings made in the dura expose the sac of the hematoma, which is torn open allowing the contents to escape. This is followed by through and through irrigation of the sac with Ringer's solution. The scalp incisions are closed without drainage."

Eight cases are reported in which the patients were treated. In the first case, with bilateral chronic subdural hematomas, the symptoms were not relieved by removal of the hematoma through a right osteoplastic craniotomy. Recovery followed subsequent simple drainage of the hematoma on the left side. Only one of the eight patients, who was "in extremis" at the time of operation, died. Six are entirely well. Two of these had bilateral hematomas. Another, also with bilateral hematomas, complains of "constant tinnitus and occasional attacks of nausea and vomiting." That this is an industrial compensation case, the authors believe, "may be of significance." They point out that "his symptoms are those commonly found with head injuries and may bear no relation to the subdural hematomata." The symptoms improved and slight headache disappeared on spinal air insufflation about five months after operation.

The authors review the important signs and symptoms in the diagnosis of the condition and point out the diagnostic value of ventriculography and of roentgen rays to show the pineal shift. An interesting case showed ipsolateral signs. The lesion was correctly localized before a second operation by ventriculography. This demonstrates the importance of bilateral exploration in suspected cases.

Admitting that "complete surgical removal of the type of hematoma under consideration is possible" and that "incomplete removal of pathological material is not an accepted surgical principle" the authors believe "that the method of simple drainage is open to criticism." Nevertheless, they emphasize certain points in its favor: "(1) A relatively minor procedure is substituted for a formidable operation. (2) Exploration anteriorly and posteriorly, as described, minimizes the possibility of overlooking such a condition which in a certain percentage of cases is bilateral. (3) A negative bilateral exploration can be followed at once by the diagnostic procedure of injecting air into the ventricular system. (4) Local anaesthesia can be employed invariably. (5) The time which is required for the operation and the tax on the patient are reduced to a minimum."

The authors conclude further that: "(1) Non-operative treatment of these patients has proved unsatisfactory. (2) Exploration through small trephine openings is a benign procedure and is indicated in suspected cases of chronic subdural hematoma. (3) Evacuation of the hematomata through small openings is efficacious. (4) In no instance has there been a recurrence of symptoms."

Four years have elapsed since the authors first used this method, and the results appear to have been satisfactory.

ELVIDGE, Montreal.

HAS THE MUSCULAR SUBSTANCE A LONGER CHRONAXIA THAN THE NERVOUS SUBSTANCE? LOUIS LAPICQUE, J. Physiol. **73**:189, 1931.

Lapicque reviews the controversy existing between his views and those of Keith Lucas and the recent work of W. A. H. Rushton. From his own more recent experiments he finds that a fresh and normal sartorius placed directly in a Ringer solution and stimulated through the solution without any direct contact with the electrodes is subject to give two very distinct strength-duration curves, one of them being spread over several hundredths of a second. This confirms Rushton's work. Lapicque now, therefore, recognizes for the muscle (placed in the conditions described) two kinds of stimulation: an α stimulation—relatively slow—and a γ stimulation—relatively quick.

When only one electrode is "fluid" and the other composed of a thin wire (stigmatic) placed in contact with the muscle in the solution, there results a pure γ curve when the stigmatic electrode is cathode, and a pure α curve (or at least most of its length) when it is anode. The same γ curves are obtained when the stigmatic cathode is placed anywhere on the muscle (whether on the pelvic part, which is nerveless, or on any other part). This is not a direct contradiction of Keith Lucas' and Rushton's experiments, as these authors have never operated under the same conditions, but it disagrees with their identification of two hypothetic substances α and γ. Curare, when applied at such doses as to cancel any

indirect stimulation and even at much higher doses, keeps the two distinct curves (with or without a stigmatic electrode). The α curve is almost entirely unchanged, the γ curve is slightly slowed down.

The results regarding α are in agreement with Keith Lucas and Rushton, while the one for γ is in formal contradiction with the conclusions drawn by these authors from their experiments, though Keith Lucas found again a rapid curve. In any case, the persistence of the curve is as much if not more than the preceding fact, in disagreement with the conception of a muscular substance α and a nervous one γ.

Further, the α curves obtained either by Keith Lucas and Rushton or by Lapicque do not possess, as a rule, the shape the latter has always found on most different kinds of excitable substances, a necessary condition for the notion of chronaxia. The author believes that they may represent another phenomenon entirely, and from recent researches can state already that the α curve seems to have less to do with the special qualities of the excitable substance than with the particular conditions realized when electric stimulation comes through a solution more conducting than the living substance itself. Thus, the main reason for the difference between Keith Lucas' results and those of Lapicque would lie in the use by the former of fluid electrodes, the muscle being more or less dipped in Ringer's solution, while in all Lapicque's previous experiments the muscle was in air, that is to say, in an insulating medium, the current entering and especially coming out at a definite point. This probably explains the two series of experimental results. It must be remembered, as Lucas himself pointed out, that "the experiments made in Ringer's fluid are in a considerable degree abnormal and artificial."

ALPERS, Philadelphia.

THE KAFKA PARAFFIN REACTION OF THE CEREBROSPINAL FLUID. W. GIRLICH, Arch. f. Psychiat. **93**:495, 1931.

The author discusses the technic and reliability of the Kafka paraffin reaction on the basis of about 1,500 case studies. The method was introduced by Kafka in 1924, and can be described briefly as follows: The stock solution consists of 0.3 Gm. of paraffin (melting point from 50 to 52 C.) dissolved in 100 cc. of absolute alcohol, heated to the melting point of the paraffin. The solution does not deteriorate for at least two months. Before the actual examination of the spinal fluid, equal parts of this stock solution and distilled water are heated to the melting point of the paraffin and then mixed in one vessel. The spinal fluid is then added to this solution. Ten test tubes are taken; 0.75 cc. of 0.3 per cent sodium chloride solution is placed in the first tube, and in each one of the remaining nine, 0.5 cc. of the same solution; then 0.25 cc. of spinal fluid is added to the first tube; when this has been shaken, 0.5 cc. is pipetted from the first tube and placed in the second; 0.5 cc. of this is placed in the third. The procedure is continued through all the tubes, so that a series of dilutions is made of ¼, ⅛, 1/16, etc., to $\frac{1}{2^{0.48}}$. To each of the tubes 0.5 cc. of the paraffin solution is added, and the resulting changes in the tubes are noted.

The reading of the changes is best made after the tubes have been allowed to stand for twenty-four hours. The changes are divided into six grades, ranging from a total lack of change in the color and consistency of the paraffin solution to a complete clearing of the fluid with flocculation on top of the fluid. Depending on the changes in different types of spinal fluids, five curves have been established: 1. The normal curve. This consists in an absence of change throughout the ten tubes. 2. The dementia paralytica curve. There is usually a change ranging between the normal state and disappearance of the color in the first tube, shading down to disappearance of the color in about the third tube, remaining there until about the fifth tube, and then gradually increasing until there is absence of change in about the seventh, eighth or ninth tube. 3. The tabetic curve, which is similar to that of dementia paralytica, except that complete change is found only in one tube and the fluid quickly returns to normal in about the fifth or sixth tube.

Two other curves are those of cerebral syphilis and meningitis, in which the change never reaches the highest degree, the fluid beginning with normal and returning to normal at about the fifth or sixth tube.

Somewhat inconsistent but nevertheless definite changes have been found in a number of organic diseases, such as multiple sclerosis, encephalitis, etc., and also in cases of dementia praecox. In other functional diseases no changes have been noted.

Comparison of the changes with those obtained with the colloidal gold and the mastic colloidal reactions shows that the paraffin reaction is not quite as delicate as the others, but that, on the other hand, it is much more reliable. The author discusses colloidal reactions in the spinal fluid in general and offers attempts at interpretation of these phenomena. He concludes that the paraffin reaction is a very valuable and reliable diagnostic factor in the study of the spinal fluid.

MALAMUD, Iowa City.

EFFECTS OF ANTIRABIC VACCINE ON CERTAIN PAINFUL CONDITIONS. L. CRUVEILHIER, J. HAGUENAU, S. NICOLAU and J. VIALA, Rev. neurol. **1**:90 (Jan.) 1932.

The authors' attention was called to the possibilities of the Pasteur treatment in other conditions than rabies by observing improvement in various conditions that had nothing to do with either rabies or the bite. They therefore practiced the Pasteur treatment on patients with divers diseases of the nervous system, especially painful conditions. Three cases are reported, in which from fifteen to twenty injections had been given in the ordinary manner.

CASE 1.—A woman, aged 48, had suffered from migraine from the age of 4 or 5 years about twice a month, and since puberty once a month, except during the nine pregnancies. The patient was followed for a number of years with various therapeutic procedures, including ligation of the left temporal artery, which relieved the condition for only two months. Radiologic castration relieved it for two years, but the condition returned with great severity and the state of the patient was pitiable. During the treatment the pains diminished progressively from the fifth injection and disappeared, and six months later she was able to work and suffered no further pains.

CASE 2.—A woman, aged 51, suffered from tabetic pains in the lower limbs, with other characteristic signs of the disease. Following the treatment, the physical signs of tabes remained unchanged but the pains had practically disappeared and the patient was walking easily. Ten months later, the improvement persisted and she was able to work.

CASE 3.—A man, aged 40 years, was wounded in 1915 by a bullet penetrating the left buttock and leaving the internal aspect of the thigh. The wound did not involve the nerve trunk, and the local pains gradually disappeared without special treatment. About December, 1930, a gradually increasing painful condition in the leg prevented the patient from continuing his work, although no physical signs were elicited. The Pasteur treatment was started, and after the eighth injection he acknowledged great diminution of the pains, which finally disappeared after the fifteenth. Five months later the pains were entirely gone. There was a slight Lasègue sign.

The method in which this antirabic vaccine works to control pain is not understood. In the rabbit such treatment increases the elaboration of antibodies, especially the agglutinins. Moreover, it brings about changes in the nervous systems of rabbits in the nature of hyperactivity of the nerve cells, with increase in mobilization of the defensive elements (lymphocytes, plasma cells, macrophages, microglia cells and proliferation of the capsule cells of the spinal ganglion cells). The histologic modifications are particularly visible in animals in which the less attenuated vaccine is used and are absent in control animals given injections of

normal spinal cord. "It would seem that the antirabic vaccine works in stimulating the defensive mechanisms of the nervous system and also by repercussion on the general condition and the humoral reactions."

FREEMAN, Washington, D. C.

THE SIGNIFICANCE OF THE COLLOIDAL GOLD REACTION AS A DIAGNOSTIC AND PROGNOSTIC AID IN NEUROSYPHILIS. FREDERICK G. NOVY, Am. J. M. Sc. **183**:401 (March) 1932.

The study reported in this article was made to determine the correlation between the clinical diagnoses and the colloidal gold reactions in untreated patients with neurosyphilis and also to discover the type of change found in patients undergoing treatment. In the relation of colloidal gold reaction to clinical diagnosis, 700 patients were investigated. There were 500 patients with various forms of neurosyphilis. As controls, 200 patients with syphilis without involvement of the central nervous system were used. In the group of latent cases, 36 patients gave entirely negative reactions, while 49 showed a maximum color change of "1," which falls well within normal limits. Eleven patients had a color change of "2," and 4 patients a color change of "3." In the congenital group (100 patients), 97 were within the normal range of reaction. Of the patients with dementia paralytica, 65 had a zone I change, with a maximum color change of "5"; 19 others presented the same type of curve, but the maximum color change was of less intensity—"3" or "4"; 9 patients gave slight changes. Of the group with tabes dorsalis, 42 patients gave normal reactions; typical curves of tabes were found in 47 patients, while the dementia paralytica was noted in 11 patients. In patients with dementia paralytica, reactions were found midway between tabes and dementia paralytica. There was no characteristic reaction in the group of patients with diffuse cerebrospinal syphilis; however, there were 15 patients with the high zone I type. In patients with dementia paralytica a similar type of reaction is most frequent. The tabetic and diffuse cerebrospinal patients tended to react in the second zone. To make a diagnosis from the colloidal gold reaction alone, therefore, is impossible; more reliance should be placed on the clinical picture. The changes in colloidal gold reaction were studied in 413 patients under treatment for neurosyphilis. Intraspinal therapy of Wile was given in 127 cases. Of the patients with tabes dorsalis, dementia paralytica and late diffuse cerebrospinal syphilis, a little over half showed no zone change following intradural therapy. Of those with dementia paralytica, less than half remained in the same zone in which they started. In the majority of patients a decrease in the intensity of the reaction was noted, which, however, was slight. Of 138 patients who received treatment with tryparsamide, a shift from one zone to another was frequently encountered. Of the 148 patients with neurosyphilis who received treatment with malaria, the shift from one zone to another was less marked, but the color change was striking. In conclusion, there was a tendency for zone I curves to change to the middle zone with all types of treatment, and for zone II curves to remain as zone II curves; there was a reduction in the maximum color intensity, which was about the same with all types of therapy.

MICHAELS, Boston.

A NEW METHOD OF EXPERIMENTAL STUDY OF TUMORS OF THE BRAIN. R. V. VOLEVICH, J. nevropat. i psikhiat. **1**:21, 1931.

The topical diagnosis of tumors of the brain is an extremely important problem in clinical neurology, and often the correct location is revealed only at postmortem examination. The only way to develop a precise method of location of tumors of the brain is to produce tumors experimentally in various areas of the brain and then study the symptoms so that a series of correlated observations can be worked out.

In 1924, Volevich offered a method of experimental production of tumors which, however, was not used by him until 1929. The method consists in

injection of paraffin into definite areas of the brain. Paraffin was chosen on account of its well known chemical inertness, and because its action is purely mechanical. The organism reacts to paraffin either by encapsulation or by permitting connective tissue and blood vessels to pass through it. In the first case the organism treats the paraffin as a foreign body; in the second a glioma is produced "at will." The melting point of the paraffin should be around 45 C. The trephine opening in the skull must be very small.

The author reports the cases of two dogs that were subjected to the experiment. In the first dog, 1 cc. of paraffin was injected into the left parietal region. Five days later, paralysis of the right hind leg developed, which improved within a week; after a month the animal became very dull, apathetic, afraid and tremulous. A subsequent injection of 4 cc. of paraffin resulted in the dog's death. Autopsy showed small lumps of red paraffin in the left lateral ventricle. Hemorrhages the size of a pinpoint were observed in the basal ganglia in the vicinity of the lateral ventricle.

In the second dog, an injection of 1 cc. of paraffin into the left parietal lobe resulted in no symptoms. Then, a little more than 1 cc. was injected into the right parietal lobe. The dog became very dull, apathetic and stupid, but showed no motor phenomena. Autopsy showed two paraffin masses lying freely in the lateral ventricles and a small mass of paraffin infiltrated in the region of the right thalamus, with layers of connective tissue and some glial tissue going through the paraffin. The author comes to the conclusion that when the paraffin passes into the ventricles it remains unchanged, but if left in the brain tissue it becomes infiltrated with various elements of the nervous system, giving rise to a true tumor.

KASANIN, Howard, R. I.

MANAGEMENT OF ACUTE BRAIN INJURIES, WITH SPECIAL REFERENCE TO THE INDICATIONS FOR OPERATION. CLAUDE C. COLEMAN, J. A. M. A. **97**:1696 (Dec. 5) 1931.

The author discusses certain observations made on a series of 596 patients who received treatment in the Hospital Division of the Medical College of Virginia during a period of five years, closing Jan. 1, 1929. The methods employed in the treatment of this group are briefly reviewed. Of these 596 patients, 453 had head injuries of sufficient severity to produce a demonstrable fracture of the skull or unconsciousness, or both. There were 275 demonstrated fractures of the skull in this series. Of the entire group, 143 are excluded from consideration here because of the fact that, although they had head injuries requiring a stay in the hospital, the injuries were of a mild type. In the group of 453 under consideration, 78 cranial operations were performed, and of these operations 32, or 7 per cent, were subtemporal decompressions, 22 on the right side and 10 on the left. In the 453 cases there were 84 deaths, a mortality of 18.5 per cent, 34 patients dying in less than twelve hours, and 50 after this period. The mortality is and probably will remain inevitably high in patients receiving severe shock from extensive damage to the basal structures and widespread laceration and contusion of the brain. A smaller group, because of high intracranial pressure due to contusion with edema and to subdural and extradural hemorrhages, will require a subtemporal decompression or some form of operation for removal of the clot. The series shows that subtemporal decompression with drainage was done in more than 7 per cent of the cases to offset intracranial pressure when there were no localizing symptoms. In the author's experience, palliative measures, such as dehydration, hypertonic solutions and therapeutic spinal puncture, cannot be advantageously substituted for subtemporal decompression with drainage in all cases of brain injury. The patients in the series who urgently needed relief from compression did better with operation, frequently combined with these more simple measures. If the use of ether anesthesia is necessary to perform a subtemporal decompression, this should be noted as a relative contra-

indication to operation; however, the urgent need for relief from pressure may nevertheless require operation. Cranial operations for trauma can generally be done with local anesthesia.

EDITOR'S ABSTRACT.

INVESTIGATION OF DELINQUENT, MENTALLY ABNORMAL GIRLS. E. JACOBI, Arch. f. Psychiat. **94**:303, 1931.

The author reports a study of thirty delinquent girls who were referred to the psychiatric clinic because of different forms of mental or emotional deviation. He is particularly concerned with the attempt to ascertain the relative importance of the constitutional and environmental factors in bringing about the states of delinquency, particularly prostitution, and the relationship between these factors and the mental abnormality noted. He comes to the conclusion that, when all things are considered, the constitution of the patient seems to play a much more important rôle than the environmental conditions. He is of the opinion that, although it is difficult in any given case to decide which one of these two factors contributes more to the final product, it seems definite that the constitutional factor is the more important. This is seen especially in feeblemindedness, and the author agrees with a number of other observers that in these cases, at any rate, the constitutional defect is more instrumental in bringing about the difficulty in adaptation. In such cases the most important symptoms are those of sexual delinquency, shiftlessness, prostitution and venereal diseases. In part of the cases investigated, psychoses such as schizophrenia and dementia paralytica have really led to the delinquency. In other cases, however, the psychoses have developed long after the first signs of delinquency have shown themselves, and have merely increased the difficulty in adaptation. The prognosis in all of these cases is, of course, much poorer than in cases of delinquency in which there is no mental disease, because the combination of the mental disturbances with the poorly constituted character does not seem to lend itself to treatment.

In all of the cases attempts were made to institute psychotherapeutic measures as well as amelioration of the environmental factors, but these were mostly unsuccessful. The study is particularly important because the cases have been observed for a long time, some of them as long as from fifteen to twenty years. The author believes that although in these cases at least there was an important constitutional factor, the only way of ameliorating the conditions is by changing the environment and placing the patients in situations that will not strain their already weakened ability to adjust.

MALAMUD, Iowa City.

ERYTHROMELALGIA AND OTHER DISTURBANCES OF THE EXTREMITIES ACCOMPANIED BY VASODILATATION AND BURNING. GEORGE E. BROWN, Am. J. M. Sc. **183**:468 (April) 1932.

The author critically reviews the original reports of Weir Mitchell on erythromelalgia in a vein similar to his recent work on Raynaud's disease with Edgar V. Allen (Raynaud's Disease: A Critical Review of Minimal Requisites for Diagnosis, *Am. J. M. Sc.* **183**:187 [Feb.] 1932.) As a modification of Mitchell's criteria the author suggests that the surface temperature increases with and parallels the burning distress. The review of the literature shows lack of consistency in the application of the primary concepts, so that only one case reported is acceptable in the original sense. The confusion in using the term erythromelalgia as a symptom instead of an entity is emphasized; however, erythromelalgia itself is not all-inclusive in its description and should embrace the concept of increase in local heat, or vasodilatation. The author studied eighty-one cases, dividing them into six groups; the first two groups alone are reported. Group 1 consists of ten cases representing true primary erythromelalgia. In all the disturbance was bilateral and in all the peripheral arteries were patent. In group 2 there are three cases of primary unilateral disturbances of vasodilatation involving either the feet or hands. The rarity of the disease is evidenced by the

incidence of approximately one case in every two hundred cases of peripheral vascular disease at the Mayo Clinic. Cases with burning pain in the hands and feet secondary to other diseases and cases in which there is paresthesia of central origin must be separated from those of the specific disease. Bilateral distribution of the objective and subjective manifestations of erythromelalgia is most essential to its identification. The necessity for exact studies of surface temperature is shown throughout the work. In conclusion, the author gives the following criteria as essential to the diagnosis of the disease: (1) bilateral burning pain in the extremities; (2) sharp increase of local heat in the affected parts, although redness, flushing or congestion may vary in degree; (3) production and aggravation of the distress by heat and exercise, and (4) relief by rest, cold and elevation.

MICHAELS, Boston.

THE FEELING OF GUILT AND ITS EFFECTS. MAX LEVIN, Ment. Hyg. **15**:714 (Oct.) 1931.

Accepting the freudian interpretation of an exaggerated feeling of guilt as the subconscious recognition of the ethical impropriety of an Oedipus complex, Levin demonstrates by case reports the mechanism of this emotion. In one case, a boy in an orphanage dreamt that he was about to be taken out (which gave him pleasure), and then suddenly was told he would have to stay after all. This, Levin postulates, is the boy's self-punishment at his guilty hatred of his father. In a similar way, another boy had fantasies in which he made much money in illegal practices, and then was sent to prison; the rebellion against society is visualized as a rebellion against paternal authority; the subsequent apprehension and punishment is presumably acknowledgment of the shamefulness of this father-hatred. A girl seemed excessively anxious to praise a mother who really mistreated her; another had hysterical attacks following an argument with her mother in which she (the patient) defied her. In each case, the reaction was a compensation for shame at an intrinsic mother-jealousy. One boy became excessively reverent after his father's death, apparently worshipping his memory. Here, too, the author was not fooled, pointing out that this was merely a sense of guilt at a subconscious jealousy or hatred of his now dead parent. Levin believes that feelings of guilt may aggravate the symptoms of dementia praecox, and cites several cases as examples. One boy seemed to indulge in mental illness as the price of a deep-seated animosity toward his father. These cases illustrate one of the beauties of the freudian interpretation: Any reaction as well as its absolute opposite can be explained by the same formula. If a boy frankly loves his mother, this is an Oedipus complex; if he frankly hates her, this is an overcompensated Oedipus complex.

Levin summarizes by stressing the importance of a desire for self-punishment consequent on a feeling of guilt. These feelings may be manifested by a desire to take unmerited blame, by various neurotic symptoms and by dreams and fantasies of punishment.

DAVIDSON, Newark, N. J.

THE RÔLE OF THE PITUITARY IN THE ETIOLOGY OF CANCER. WILLIAM SUSMAN, Brit. M. J. **2**:794 (Oct. 31) 1931.

"The ideas expressed in this work," says the author, "gradually evolved during a histological survey of the whole endocrine system—on the pituitaries, thyroids, and adrenals, of over 200 cases and on the parathyroids, thymuses and pancreases, of about 100 cases or over." The histologic examination of the pituitary gland in cases of cancer suggested: (1) that the anterior pituitary was overactive and was stimulating growth, and (2) that the lesions in the posterior pituitary gland probably affected the quality and quantity of the posterior secretion, and because of this, in cases of cancer, the growth-restraining influence was inadequate. No consistent significant changes were observed in the thyroid or parathyroid glands. In 14 cases of cancer (excluding cancer of the pancreas) observed in 170 cases

in which the pancreas was examined, the islets were very numerous in 6, and in only 2 cases was their incidence normal. In all except 2 cases the islets were enlarged. This was interpreted to mean that in cases of cancer there is an increased demand for carbohydrate.

Another important part of the study was an attempt to test aforementioned findings experimentally by producing epitheliomas in mice. One hundred animals were painted with shale oil twice weekly. Their diets varied. The incidence of epitheliomas appeared to show that the presence of an abundant supply of dextrose does promote the development of epitheliomas in mice. Of the animals which did develop epitheliomas, some were treated with a solution of the pituitary gland given internally, while others were used as controls. There was definite evidence that the solution tended to cause sloughing of the tumor tissue and checking of its growth.

The last part of the investigation was clinical and definitely tended to confirm the observations and assumptions of the autopsy material and the experimental work with mice.

FERGUSON, Niagara Falls.

BLOOD-SUGAR STUDIES IN ABNORMAL MENTAL STATES. P. K. MCCOWAN and J. H. Quastel, Lancet **2**:731 (Oct. 3) 1931.

A study of the sugar tolerance curves of 85 psychotic patients was made. A hyperglycemic index (H. I.) is defined, which is a quantitative measure of the departure of a sugar tolerance curve from that found in the normal person. There is a close parallelism between the emotional tension and the magnitude of the H. I. in the manic-depressive group of patients. Of 43 melancholic patients examined, only 7 gave a normal or slightly abnormal index. A large number exhibited an index of over 50. The authors believe that there is an interference with carbohydrate metabolism secondary to the bodily changes that accompany emotion. Emotional tension may be accompanied by an outpouring of epinephrine as a defensive mechanism, and the presence of this substance in the blood would certainly account for the sustained hyperglycemia after injection of sugar. In some of the few cases of mania studied, contrary to most other observers, the writers found an increased H. I., which paralleled the psychogalvanic reflex observations. This was especially true if the excitement was accompanied by an aggressive, paranoid mood. In cases of benign stupor a low index has been recorded, showing that the defense mechanism of the stupor reaction had succeeded in abolishing the emotional tension. In the schizophrenic reaction type only a few patients showed an H. I. consistently above 50. High figures were always associated with some physical disturbance, such as toxemia or endocrine imbalance. Arteriosclerosis *per se* was not found to be a cause of a high H. I.

The significant contribution of this work is the apparent relationship between emotional tension and the hyperglycemic index. Thus, in depressed patients it might be used as an aid in following treatment and progress. The prognostic aid which is claimed seems more doubtful.

BECK, Buffalo.

TULAREMIC LEPTOMENINGITIS. REPORT OF A CASE. ARTHUR R. BRYANT and EDWIN F. HIRSCH, Arch. Path. **12**:917 (Dec.) 1931.

Tularemic lesions of the leptomeninges, contiguous brain tissues, ependyma, subependymal tissues and choroid plexus of a man dying on the sixteenth day following laceration of a finger by contact with a rabbit bone had the histologic structure of similar lesions in the liver, spleen and lungs, and corresponded structurally with those described in the visceral tissues of susceptible hosts dying with Bacillus tularensis infection. The lesions grossly resembled miliary tubercles, although their distribution was chiefly over the vertex and sides rather than along the base of the brain, and consisted of exudates of monocytes and polymorphonuclear leukocytes with varying degrees of necrosis. Where the meningeal lesions encroached on the brain, the tissues of the latter were necrotic and infiltrated by exudate cells.

In addition to the focal lesions of the meninges there was a diffuse, acute exudative meningitis. Widely disseminated lesions of the brain were not demonstrated.

Although, generally speaking, the lesions of tularemia mimic those of tuberculosis, it is unlikely that the reactions found in the meninges of this patient were tuberculous, because: (1) they repeated in minute detail the structure of lesions found in the spleen, and suspensions of this crushed tissue killed guinea-pigs in five days and produced in them visceral lesions characteristic of tularemia; (2) the search for acid-fast bacilli in the lesions of the meninges, liver and spleen was not successful, and (3) lesions of a frankly tuberculous character were not found by thorough gross and histologic examinations of the viscera.

WINKELMAN, Philadelphia.

THE MEASUREMENT OF THE PSYCHOTIC AGE. GEORGE GARDNER, Am. J. Psychiat. **10**:963 (May) 1931.

By paralleling the development of thought and behavior at age levels in infancy with the actions and thoughts of the insane suffering from psychoses with varying degrees of intensity, Gardner hopes to measure the extent of a psychosis on a chronologic developmental basis. An infant at the age of 3 months sleeps most of the time, has no bladder or bowel control, has no cognizance of an outside world. So, a simple schizophrenic patient who is motionless and incontinent and has no contact with others is assigned a psychotic age of 3 months. At 6 months, an infant tends to grimace and pick up mannerisms, to play by himself and to imitate the sounds of others; the hebephrenic person, with silliness, indifference and echolalia, is accordingly classified at a 6 month level. At the age of 1 year, a baby indulges in bouts of rage, in temper tantrums in which he may refuse to eat or in which he may stiffen. He likes to chatter and babble unintelligibly; the corresponding psychotic behavior is seen in the excitement and babbling of the catatonic patient, whose psychotic age is established as 12 months. As the child grows older, he learns to sulk, resents his parents' instructions, feels misunderstood, and becomes self-centered. Translated into psychiatric language, this is the paranoid personality.

From this point of view, a psychosis analogous to a developmental defect rather than to a clinical disease entity. Gardner considers several explanations for this — innate defect, fixation in the course of psychic development and regression. The author believes that a defective sympathetic nervous system is inherited and is acted on by stimulating environmental factors.

DAVIDSON, Newark, N. J.

INFLAMMATION OF THE GRAY SUBSTANCE OF THE CEREBRAL TRUNK (SUPERIOR AND INFERIOR POLIOENCEPHALITIS) AFTER ANTIRABIC VACCINATION. STEFAN LEŚNIOWSKI, J. de neurol. et psychiat. **31**:427 (July) 1931.

The author presents a case which he believes to be the only certain case of encephalitis following antirabic vaccination. The patient, bitten by a dog that did not have rabies, was nevertheless treated by antirabic vaccine. Dizziness and headache developed seven days after the last injection, followed later by insomnia, hyperacusis and photophobia. The patient also had paresthesias of the fingers and right side of the face. Neurologically, there were bilateral ptosis, some swelling of the right side of the face and of the right half of the mouth, sensory paralysis of the face, peripheral left facial paralysis, a positive Romberg sign and a slightly staggering gait. Examination of the spinal fluid gave essentially negative results. Later, a slight rigidity of the neck and a positive Kernig sign developed. From this status the patient gradually improved, until he was discharged apparently well.

In an analysis of the literature, it is supposed that most of the number of reported cases of encephalitis are really cases of aborted or modified rabies. The

author concludes that among the different clinical forms of illness after antirabic vaccination there may occur rarely polioencephalitis, which has a good prognosis; that the cases previously reported are largely of atypical rabies, and that paralytic attacks may result from the activation of a latent neurotropic virus, such as that of epidemic encephalitis, by the disturbance of some defensive mechanism the result of vaccinal injections. WAGGONER, Ann Arbor. Mich.

ROENTGENOTHERAPY OF TUMORS OF THE BRAIN. A. BÉCLÈRE, Rev. neurol. **2**:567 (Nov.) 1931.

Normal brain tissue is rather insensitive to the roentgen rays with the exception of the choroid plexus, irradiation of which is followed by a marked drop in the production of cerebrospinal fluid. In glandular tumors of the hypophysis the results are sometimes striking, but in suprasellar tumors, meningiomas, etc., there is little effect. Gliomas vary considerably in radiosensitivity, the medulloblastomas being the most sensitive, whereas temporary effects are observed in the spongioblastomas and relatively little in the astrocytomas. The roentgen rays are often used with good effect following partial extirpation of a tumor, but they never completely arrest the evolution of the tumor except possibly in certain gliomatous cysts. Palliative action on the acoustic neurinomas is noted, but the meningiomas are resistive. Metastatic tumors are slightly benefited. On the whole, roentgen therapy after surgical intervention is often effective in reducing the symptoms and in prolonging the life of the patient. Roentgen therapy may also be used in cases in which a tumor is suspected but not verified. The manner of action is not the same on tumors of the brain as it is in certain more accessible tumors. It would seem that without destroying completely the neoplastic element the roentgen rays would prevent or slow their multiplication. Moreover, the reduction in the formation of cerebrospinal fluid may play a considerable part in the favorable results shown by roentgen therapy. Very penetrating rays, heavily filtered and introduced from various angles, are preferred, although the reactions may be severe or dangerous. Maximal doses are favored. FREEMAN, Washington, D. C.

OCULAR CONVERGENCE: ITS RELATION TO BASAL METABOLISM AND ENDOCRINE DISEASE. LEO L. MAYER, Arch. Ophth. **6**: 389 (Sept.) 1931.

The matter of ocular convergence is a subject of definite interest to the neurologist. In all modern textbooks relating to general medicine, the endocrine glands, ophthalmology or neurology, mention is made of the so-called Möbius sign of insufficiency of convergence in exophthalmic goiter. The author quotes Price, who stated, "Various symptoms have been associated with exophthalmos, and although they do not add materially to the ease or certainty of diagnosis they are traditions of medicine." Further, he quotes Wentworth, who in a discourse on ocular signs in goiter, gave the following figures concerning the frequency of Möbius' sign: in hyperplastic toxic goiter, 10.2 per cent; in toxic adenoma, 40.9 per cent, and in nontoxic conditions, 14.3 per cent. These figures represent the percentage of cases that showed a convergence near point greater than 9 cm., approximately 3½ inches, from the base of the nose. In their entire series of 100 cases, a convergence near point greater than 9 cm. was found in only 19 per cent.

In studying a series of 150 cases of endocrine disease, the author attempted to answer various questions that logically arise relative to the convergence near point in impending exophthalmic goiter, or in well established exophthalmic goiter. In his conclusion the author states that conclusive evidence is not obtainable from such a small series of cases. He demonstrated, however, that poor convergence is definitely connected or presented in a patient with a high basal metabolic rate.

SPAETH, Philadelphia.

THE CUTANEOUS HISTAMINE REACTION AS A TEST FOR COLLATERAL CIRCULATION IN THE EXTREMITIES. G. DE TAKÁTS, Arch. Int. Med. **48**:769 (Nov.) 1931.

Instead of the usual "vaccination" technic, de Takáts introduces histamine by intradermal injection; 0.1 cc. of a 1:1,000 solution of histamine acid phosphate is used. The reactions are graded as marked (3), fair (2), faint (1) and absent (0). Sites of inoculation are the dorsum of the foot, the side of the ankle, the middle of the calf and the upper third of the thigh. The response can be taken as a measure of the adequacy of the circulation. Reactions may be noted every five minutes for four readings, but usually a single ten minute scoring is satisfactory. In fifty normal subjects, all parts of the extremity gave reactions of 2 or 3 within ten minutes, the toes and malleoli showing sluggish responses. Twenty-five patients with occlusion of the artery (mostly from diabetic gangrene or Buerger's disease) were studied, and in almost every case, 0 reactions were obtained below the knee. The histamine test also served as a guide to therapeutic efficacy, as when treatment brought about improvement the flare became visible lower down on the leg. The cutaneous reaction is a guide to amputation limits, as a negative response indicates that circulation will be inadequate to nourish the stump. In early cases of arterial occlusion the histamine flare was diminished or absent in the ankle and foot. Persons who had spasms of the peripheral arteries (as in Raynaud's disease) show a delayed or negative response in the legs and feet, which promptly improved following immersion in hot baths.

DAVIDSON, Newark, N. J.

A CONTRIBUTION TO THE STUDY OF THE REACTION OF TAKATA-ARA. J. SALAS, L. NAJERA and L. FANJUL, Arch. de neurobiol. **11**:128 (March-April) 1931.

The authors have studied the reaction of Takata-Ara in the cerebrospinal fluid in 480 cases, including essential epilepsy, schizophrenia, epidemic encephalitis, senile dementia, meningitis, dementia paralytica and human trypanosomiasis. In addition, the normal cerebrospinal fluid has also been investigated. The mechanism of the reaction is analyzed and it is concluded that it is a very complex one, since many factors are involved. On the strength of their experiments the authors advance the following interpretation, which they regard as a working hypothesis: The mixture of fuchsin and sublimate in an alkaline medium shows a violet color. In an acid medium it appears pink. A type II reaction is obtained because the proteins and acid ions fix all of the carbonate and the medium remains acid. In dementia paralytica, and in the normal cerebrospinal fluid the proteins present in the fluid do not occur in sufficient amount to fix all of the carbonate; the medium, in such cases, is alkaline and the color changes to bluish-violet. Finally, the flocculation, which may occur in the acid zone (mixed type) or in the alkaline zone (syphilitic type) depends on the quality of the proteins in the fluid. Globulins produce a maximum of precipitation. The experiments carried out by the authors do not permit a decision as to whether flocculation in the acid and the basic zone is produced by different kinds of proteins.

NONIDEZ, New York.

THE POSTMORTEM CHANGES OF THE MICROGLIA. A. KÁLLÓ and V. DUBRAUSZKY, Riv. di neurol. **4**:84 (Feb.) 1931.

Following the investigations of Vizioli on the postmortem changes of the microglia in animals, the authors undertook a study of the postmortem changes of microglia in man and reached the conclusion that they consist of a gradual rarefaction of the cytoplasm surrounding the nucleus, which appears pyknotic, and in a gradual deformity and breaking down of the cellular prolongations. The authors have never found vacuolization, liquefaction, ameboid transformation or hypertrophy of the microglia as an expression of postmortem changes.

The temperature has considerable influence over the process of autolysis, and at 0 C. the postmortem changes begin ten hours after death. Between 18 and 20 C.

the changes occur after eight hours, and at a temperature of from 37 to 42 C. the changes occur between four and five hours after death. The autolytic process requires fifty-eight hours at 0 C. to run its entire course, whereas, at 20 C. it requires twenty-eight hours to complete the postmortem changes. Another point is that the microglia in the white substance seem to be most resistant, as autolysis at 0 C. does not begin in these microglia until fourteen hours after death. Autolysis occurs also in pathologic brains in which autolytic changes are added to the pathologic changes of acute swelling or liquefaction brought about by the pathologic condition.

FERRARO, New York.

CUMULATIVE EFFECTS OF INFINITESIMAL DOSES OF LEAD. NORMAN PORRITT, Brit. M. J. **2**:92 (July 18) 1931.

The author, who himself had suffered from two attacks of plumbism produced by minute doses of lead over a long period, describes three other cases also, and cites the fact that one of the patients, a physician, discovered ten cases among his patients. In these cases, characterized by a slow, subtle, insidious onset, there are few, if any, of the classic symptoms of plumbism, rarely colic, seldom a blue line on the gums, rarely noticeable anemia and wrist-drop only if the condition is allowed to progress unrecognized. The usual symptoms are lethargy, loss of interest and weariness of flesh, progressing to the stage where the patient feels gloomy and taciturn, and sits silent and apathetic, his faculties and bodily powers sluggish. Sleep brings welcome respite, but he awakens in the morning tired and weary. Mild gastro-intestinal symptoms may be present. The complexion is fresh and healthy. A diagnosis can and should be made only from a careful chemical examination of the patient's urine. Plumbosolvent water is rather common in moorland regions, particularly because of an acid derived from the peat. In these districts the mortality from eclampsia is very high as compared with that in London. The author thinks that this type of plumbism is a potent cause of an increase in mortality rate. No medicinal treatment is necessary to expel lead from the system. Symptoms cease when the plumbosolvent water is either stopped or filtered.

FERGUSON, Niagara Falls, N. Y.

THE FORM AND GRAY CONNECTIONS OF THE HUMAN CLAUSTRUM. GIUSEPPE PINTUS, Arch. gen. di neurol. psichiat. e psicoanal. **12**:16 (March 31) 1931.

In a previous work the author studied the cyto-architecture of the claustrum. Here he deals with the form and gray connections of this formation in man. He reviews the anatomic studies made by various authors. He describes the claustrum in verticofrontal, sagittal and horizontal sections, and summarizes his conclusions as follows: The claustrum is a concave, laminar formation, thicker in the center than at the edges, with irregular, sometimes thick and sometimes thin, edges; it is of homogeneous structure, except in the area of the antero-superior angle, where the fibers of the fasciculus uncinatus run through the claustral gray matter. The claustrum has gray connections with the nucleus amygdalae; they consist of a few bridges of ganglion cells joining both formations. The gray connection of the claustrum with the cortex of the insula is very indistinct; only in a few sections does one see rare claustral cells scattered through the capsula extrema, the latter also containing the cells of the sixth layer of the insular cortex; this, however, does not indicate that there exists a direct continuity between claustrum and insula. No gray connections are found between the claustrum and the putamen or between the claustrum and other basal gray formations.

YAKOVLEV, Palmer, Mass.

LIPOID HISTIOCYTOSIS (NIEMANN-PICK'S DISEASE). BENJAMIN WASCOWITZ, Am. J. Dis. Child. **42**:356 (Aug.) 1931.

Another case of lipoid histocytosis is reported in detail, the condition occurring in a girl infant, aged 7 months, who was born of Jewish parents, consanguineously

related, the father being the uncle of the mother. The patient lived until the age of 15 months and died of terminal bronchopneumonia. She was manifestly mentally retarded. Examination revealed an extremely large liver and splenic area, and puncture of the spleen revealed the typical "foam cells." There was also a cherry red spot on each fundus, but there was no spasticity of the extremities or hyperacusis. Autopsy revealed the usual waxy and "rubbery" condition of the entire brain. Dr. J. H. Globus reported that the general appearance of the brain was typical of amaurotic family idiocy.

Reference is made to the belief of Bernard Sachs that the underlying process in both conditions is a lipoid cellular degeneration; that in Tay-Sachs' disease the morbid process is limited to the central nervous system and in Niemann-Pick's disease is developed as an unusual lipoidal degeneration, in which the nervous system may be involved to a varying degree or not at all.

Dr. H. G. Poncher has reported another case of the disease.

LEAVITT, Philadelphia.

CEREBRAL TUMOUR AS A CAUSE OF GENERALIZED EPILEPTIC ATTACKS OF LONG STANDING. E. A. BLAKE PRITCHARD, Lancet **2**:842 (Oct. 17) 1931.

Five cases of cerebral neoplasm are presented in detail, which show that it is possible for a cerebral tumor to give rise to generalized convulsions and even to status epilepticus for many years. One patient had a large subcortical glioma in the left occipital and posterior parietal lobes, with a history of epileptic seizures for eighteen years before any signs indicating a local cerebral lesion were detected. In general, it may be stated that such tumors are of slow growth and originate not in, but beneath, the cerebral convolutions. The attacks cannot rightly be regarded as resulting from a rise in intracranial pressure; first, since they may be present for many years before other signs of such a rise are evident, and second, because they do not necessarily increase in frequency or in severity when a rise in intracranial pressure later supervenes.

The inference drawn from these considerations is that when convulsions commence and occur repeatedly in persons of middle age, even though the convulsions are generalized in character and leave behind them no local impairment of function, they should be regarded as possibly resulting from an intracranial neoplasm. The patient should be kept under observation, for only after several years may definite signs be discovered indicating the true etiology of the convulsions.

BECK, Buffalo.

RESULTS OF TREATMENT OF THROMBO-ANGIITIS OBLITERANS BY FOREIGN PROTEIN. NELSON W. BARKER, J. A. M. A. **97**:841 (Sept. 19) 1931.

From a study of the effects of foreign protein therapy in 150 cases of thromboangiitis obliterans, Barker concludes that this form of treatment is chiefly valuable to carry a patient through one of the critical periods of exacerbation, provided gangrene has not already become too extensive. Once he has been carried through such a period, other measures should be substituted. These include education regarding the disease; protection of the extremities from mechanical, thermal and chemical injury; special hygiene, particularly of the feet; limitation of activity; abstinence from tobacco; postural exercises; contrast baths, and sympathetic ganglionectomy in selected cases. In certain cases in which ulcers or limited gangrene are present, and in which healing is well established following treatment by foreign protein, sympathetic ganglionectomy will markedly accelerate the process of healing. Treatment by foreign protein is rational for thrombo-angiitis obliterans. It tends to relieve pain and give increased blood supply to the extremities, thus accelerating the healing of open lesions. It has relatively little effect in cases in which there is claudication only or in cases in which there is extensive gangrene. The best results are secured in cases in which there is rest pain, with or without ulcers or limited gangrene.

EDITOR'S ABSTRACT.

INDISPENSABLE USES OF NARCOTICS: CHEMISTRY OF BARBITAL AND ITS DERIVATIVES. GEORGE W. COLLINS and PAUL NICHOLAS LEECH, J. A. M. A. **96**:1869 (May 30) 1931.

Collins and Leech believe that the increased use of hypnotics undoubtedly has been due in large measure to the zeal with which pharmaceutic houses vie with one another in introducing new, though not dissimilar, proprietary synthetics having sedative properties. Today, barbital and its derivatives are by far the most widely used. Yet it was scarcely a century ago that the first synthetic substance to be used as an hypnotic was prepared, namely, chloral hydrate. Liebig discussed its chemistry in 1832, but it was not until 1869 that Liebreich reported extensively on its pharmacologic action. Since then there have been many contributions to hypnotics before the present-day popularization of the barbital class. The authors present a brief and relatively nontechnical review of the chemistry of barbital and its derivatives. In order that the reader may easily visualize the relationship of the barbitals, there is appended here a chart showing the structural differences and their respective melting points. It will be noted that the compounds, chemically speaking, are probably more closely related than any other large group of essentially similar pharmaceuticals.

EDITOR'S ABSTRACT.

ALTERATIONS OF THE SYMPATHETIC CELLS OF THE HUMAN SUPRARENAL GLAND. J. M. ORTIZ PICON and A. GALLEGO GARCIA, Arch. de neurobiol. **11**:121 (March-April) 1931.

This paper deals with alterations observed in the ganglion cells of the medulla of the suprarenals. The man under observation had died of cancer of the rectum; other lesions of an inflammatory nature had also occurred. Sections were stained with Rio Hortega's method for the staining of nerve cells and nerve fibers (double impregnation with silver nitrate and silver carbonate). The more pronounced alterations consisted of changes in the neurofibrils, accompanied by slight cell atrophy, and, in many cells, an excess of pigment. Along the course of the neurofibrils and, in most cases, outside the cells, there were rings interpreted by the authors as arising through fragmentation and curling of the neurofibrils. A similar curling and fragmentation gave rise to more irregular formations similar to skeins. In addition there were spherical masses of deeply stained material and club-shaped processes which were regarded as being due to condensation and degeneration of the neurofibrillar substances. Many of the club-shaped processes were intracapsular; that is, they arose from intracapsular dendrites and were in some cases closely applied against the cell body. The pathogenesis of the changes observed in the ganglion cells is unknown. A short discussion ends the paper.

NONIDEZ, New York.

PSEUDO-ARGYLL ROBERTSON PUPILS WITH ABSENT TENDON REFLEXES, A BENIGN DISORDER SIMULATING TABES DORSALIS. W. J. ADIE, Brit. M. J. **1**:928 (May 30) 1931.

The author calls attention to a benign, symptomless disorder characterized by pupils that react in accommodation but not to light, and by absent tendon reflexes. The true Argyll Robertson pupil reacts promptly and fully, often excessively, on convergence, and dilates again as soon as the effort to converge the visual axes is relaxed. In the cases described illustrative of this benign, symptomless disorder, the pupils do not respond to light; they contract very slowly through a wide range during a sustained effort to converge; they often remain small long after the effort ends, and when they dilate again, do so slowly. Five cases are reported from personal observation by the author, and one case is quoted from the literature. All showed this peculiar pupillary phenomenon and in addition either absent or diminished tendon reflexes. One case had shown these symptoms twelve years

previously. In all cases, there was neither clinical nor serologic evidence of syphilis. No explanation is given of the etiology or the mechanism of this phenomenon.

FERGUSON, Niagara Falls, N. Y.

MENTAL HEALTH AS A NATIONAL PROBLEM. RAY LYMAN WILBUR, Ment. Hyg. **15**:449 (July) 1931.

After emphasizing the growing importance of mental hygiene in a world of progressing complexity, Wilbur points out the road to a solution of the problem. A larger and more adequately trained personnel is the first objective. Psychology and psychiatry must be applied to daily life, as for example to the selection of a career; intelligent guidance in this one department alone would contribute much to personal stability and individual happiness. Standards must change, and the common concept of mental disease as a sort of wilful crime must be replaced by the knowledge of mental disease as an unfortunate illness; the patient who has become acutely psychotic should find himself in a hospital, not a jail, and his first contact should be with a physician and not a policeman. Internship in a mental hospital should be demanded for physicians, not only to broaden the student's knowledge of psychiatry, but also to stimulate psychopathologic research by members of the hospital staff. More of the time, money and energy devoted to clinical and laboratory research should be devoted to a study of mental hygiene.

DAVIDSON, Newark, N. J.

PARANOID HALLUCINATORY STATES IN CONNECTION WITH THE MALARIAL TREATMENT OF DEMENTIA PARALYTICA. A. M. NEMIZOVSKY and I. V. NAZBUTOVICH, Rev. psychiat., neurol. & reflexol. (Leningrad) **5**:16, 1930.

In his review of malarial therapy in 1925, Gerstman pointed out that the clinical picture of dementia paralytica is changed considerably after treatment with malaria. He stated that one observes hallucinations, especially those of the auditory kind, and delusions of persecution, probably due to the endarteritis. When delusions and hallucinations appear for only short periods of time in the course of treatment, the prognosis is favorable. When they become chronic, the prognosis becomes unfavorable. The author cites illustrative histories of patients, under treatment with malaria, in whom delusions and hallucinations developed. A careful study of these cases shows evidences of previous alcoholism, and the onset of the psychosis, with delusions of infidelity and auditory hallucinations, suggests that alcohol may be a more important factor than the infection. Cases in which there is a mixture of alcoholism and schizophrenic symptoms do not react favorably to treatment.

KASANIN, Boston.

TWO CASES OF POLYNEURITIS, PARACELLULAR AND TRANSITORY, OF FAVORABLE EVOLUTION. A. DELHAYE, J. de neurol. et psychiat. **31**:521 (Aug.) 1931.

The author describes two cases of polyneuritis. The first was that of a patient with an undiagnosed, afebrile, influenzal condition, followed by the development of polyneuritis, which simulated Landry's disease in its manner of progression, and was associated at one time with almost complete muscular paralysis and sensory disturbance and also with clinical evidence of meningeal irritation. The patient recovered within forty-five days. The second case was very similar and followed an attack of influenza and bronchopneumonia. This patient also showed muscular paralysis, although not as generalized as the first patient. She also showed clinical evidences of meningeal irritation and of sensory disturbances. This patient showed much more rapid recovery, with the disappearance first of paresthesias and hyperesthesias and of meningeal signs, followed by the return of tendon reflexes. The author believes that the symptoms resulted from some form of neurotropism which disappeared shortly after the precipitating factor had cleared up.

WAGGONER, Ann Arbor, Mich.

THE GRAY COMMISSURE, AN ANATOMICOCLINICAL STUDY. FERDINAND MOREL and J. WEISSFEILER, Encéphale **26**:659 (Nov.) 1931.

The gray commissure, considered by some authors as an organ of regression, appears to be constant in the mammalia. The absence of this structure is a characteristic of human beings, more particularly of the male sex, in which it is absent in 27 per cent of cases compared with only 10 per cent absence in the female. Thus, it is in some ways an indication of a sex characteristic of the brain. In three groups of diseases of the brain there was found the same proportion of cases of agenesis of the gray commissure, i. e., in chronic hallucinatory psychosis, dementia paralytica, and senile and arteriosclerotic dementias. In alcoholic disorders of the delirium tremens or Korsakow types there appears a lack of the gray commissure in about 50 per cent of cases; in idiocy, dementia praecox and Huntington's chorea there were no cases of agenesis; occasionally the gray commissure was missing in juvenile epilepsy. The authors believe that this subject should be investigated as a routine. ANDERSON, Los Angeles.

THE ANTERIOR LOBE OF THE HYPOPHYSIS AND GROWTH. P. VON MONAKOW, Schweiz. Arch. f. Neurol. u. Psychiat. **27**:321, 1931.

Monakow reports a case of infantilism with mental retardation in a boy, aged 7, with a mongoloid facies, who for the preceding four years had been successfully treated with a hypophyseal preparation. When first seen at the age of 6, the patient was thought to be suffering from hypothyroidism. He began to grow after the institution of thyroid medication, but the rate of growth, though normal at first, gradually became slower until his fourteenth year, when it was practically in abeyance. Treatment with thymus and various hypophyseal preparations had been ineffective. Immediately after the institution of treatment with anterior lobe substance prepared from the hypophyses of growing animals, the patient began to grow at twice the normal rate and to develop sexually, although he remained mentally retarded. Monakow expresses the belief that the results of treatment do not warrant the conclusion that the infantilism in this case was necessarily attributable to a hypofunction of the hypophysis.

DANIELS, Rochester, Minn.

THE PRODUCTION OF HYPERPLASIA OF THE THYROID GLAND BY CHEMICAL MEANS. W. H. COLE, N. A. WOMACK and W. H. ELLETT, Arch. Surg. **22**: 926 (June) 1931.

In infectious diseases, the authors noted hyperplasia of the thyroid gland which, they postulated, was due to stimulation of this organ by toxins liberated as a result of bacterial catabolism. To verify this experimentally they administered histamine and xanthine to dogs and noted in each case hyperplasia of the thyroid, with epithelial desquamation and loss of colloid. Guanine produced no change, nor did uric acid. Significant results were found following the administration of caffeine, theobromine and theophylline. Definite hyperplasia occurred, the changes in many cases being similar to those seen in exophthalmic goiter. Many inorganic drugs, such as copper sulphate, were given, but in no case was the thyroid altered. The authors conclude that the toxic goiters of human beings represent stimulation of the thyroid gland by the by-products of protein catabolism.

DAVIDSON, Newark, N. J.

MENINGEAL PERMEABILITY. GINO CALZAVARA, Rassegna di studi psichiat. **20**: 694 (July-Aug.) 1931.

In order to establish whether the chromoneuroscopic test of Flatau may be influenced by the use of drugs having an influence on the hemato-encephalic barrier, Calzavara used substances acting on the sympathetic and parasympathetic systems, as for instance, pilocarpine. In a second group of cases he tested the action of

substances with a vasodilating influence; in a third group he used calcium administered intravenously, and in a fourth group glandular products (thyroid and prehypophysis).

The results of the investigations lead the author to conclude that in regard to the passage of fuchsin into the cerebrospinal fluid the action of pilocarpine, calcium, sodium nitrite and glandular products is practically nil. Consequently, on the basis of Roberti's conclusions and his own findings, the author advises the abandonment in man of the use of the Flatau test with acid fuchsin.

FERRARO, New York.

DECEREBRATE RIGIDITY IN THE CLINIC. AUSTREGESILO and MARQUES, Encéphale **26**:756 (Dec.) 1931.

Decerebrate rigidity is a syndrome of relatively frequent occurrence in neurologic services. It can appear as the result of lesions of the following systems: corticostriatal, pallidostriatal, pedunculopontile, indirect cerebellar and bulbar. The causes are almost as diversified as pathology of the brain itself—intoxication, inflammation, degenerative changes, thrombosis, hemorrhage and tumors. Even psychogenic alterations may, in the opinion of certain authors, be responsible. Symptoms are the more or less classic ones of hypertonic extension of the antigravity and the Magnus-de Kleijn reflexes. These latter phenomena are not indispensable, however, to the diagnosis of decerebrate rigidity. The authors then describe four cases presenting this picture. Two are infantile encephalopathies, one Little's disease, and one of especial interest because in many ways it is classic hysteria. The authors believe that there is probably associated a chronic encephalitis.

ANDERSON, Los Angeles.

SOME COMMON COMPLAINTS AMENABLE TO SPINAL TREATMENT. THOMAS MARLIN, Brit. M. J. **2**:746 (Oct. 24) 1931.

Favorable results are reported in the following conditions treated by spinal manipulations: coccyalgia, sciatica, lumbago, sacro-iliac conditions, stiff back and neck, intercostal neuralgia, headaches, constipation, indefinite gastro-intestinal conditions, herpes zoster and asthma. The author asserts that any attempt to explain such results must be highly speculative. He discounts the theory of pressure and impingement from luxated or dislocated vertebrae and has been unable to demonstrate such a pathologic condition by the roentgenogram. That the treatment is psychologic is not considered probable in the light of the author's experience. That there was a change in the state of the tensioned tissues was demonstrated in many cases. That changes may be due to some alteration of the sympathetic nervous system is considered a possibility.

FERGUSON, Niagara Falls.

THE FEEBLEMINDED PROBLEM. WALTER M. ENGLISH, Am. J. Psychiat. **11**:1 (July) 1931.

Dr. English's presidential address at the meeting of the American Psychiatric Association in 1931 is a plea for sterilization of the feebleminded. He is of the opinion that the great majority of cases of mental disease are the result of heredity, although no evidence is cited in support of this contention. He calls attention to the general increase of mental deficiency, showing that between 1906 and 1928 the incidence of feeblemindedness in England increased from 4 to 8 per thousand. English does not, however, mention the corresponding increase in diagnostic skill as the result of improved laboratory and psychometric testing during that period. To control the spread of feeblemindedness, he recommends sterilization, believing that segregation is impracticable. He concludes by quoting judicial opinion upholding the legality of eugenic sterilization laws.

DAVIDSON, Newark, N. J.

HERPES ZOSTER AND VARICELLA: CONVALESCENT SEROTHERAPY. L. CORNIL and F. BLANC, Rev. neurol. **2**:123 (July) 1931.

The patient's illness began on December 12 with right facial neuralgia, which was followed on December 14 by a mild chickenpox eruption. Five days after the onset of pain, herpetic vesicles appeared in the first and second divisions; on December 20, there was severe generalized varicella; on December 31, there was complete ophthalmoplegia. A recurrence of facial neuralgia, with neuroparalytic keratitis occurred on January 12; there was a mild recurrence of varicella in March. On December 22, while the varicella was at its height, 20 cc. of blood from a patient convalescing from herpes zoster was injected subcutaneously, with complete relief of pain and a marked turn for the better. The close relationship between herpes zoster and varicella is again emphasized by this case.

FREEMAN, Washington, D. C.

MINERS' NYSTAGMUS. W. J. ROCHE, Brit. M. J. **2**:55 (July 11) 1931.

A comparison of the incidence of miners' nystagmus in miners working on the same seam in two different pits about a mile apart is given on the basis of those receiving compensation. In pit A, 0.303 per cent received compensation for nystagmus, while in pit B, 1.27 received compensation. In pit A, 26.25 per cent suffered from nystagmus, while in pit B, 41.42 per cent were affected. A comparison of the reflecting power of the coal faces in each pit was established. The face in pit A was decidedly higher in its reflecting power. Other comparisons being essentially the same, this study tends to corroborate the theory that insufficient illumination producing peripheral rather than macular vision is the cause of miners' nystagmus. Recommendations are given to correct the causes of this difficulty.

FERGUSON, Niagara Falls, N. Y.

PERITONSILLAR ABSCESS AND MYDRIASIS. T. and S. HORNING-WENGER, Rev. d'oto-neuro-opht. **9**:580 (Oct.) 1931.

In patients of all ages with unilateral quinsy, the homolateral pupil was found to be dilated. The sign is clearer when the distention from the abscess is greater. The authors have had the experience of draining the abscess and seeing the mydriasis disappear; when iodized poppy-seed oil 40 per cent was injected into the abscess cavity, the sign reappeared. A roentgenogram showed the cavity to be watertight, with complete closure toward the tissues of the neck. The mydriasis again disappeared when the cavity was emptied anew; the mechanism of its production is either by direct irritation of the sympathetic system or by a "repercussivity" of bulbar origin.

DENNIS, Colorado Springs, Colo.

COLLOIDAL THORIUM DIOXIDE PREPARATION IN ARTERIAL ENCEPHALOGRAPHY. EGAS MONIZ, PINTO and LIMA, Rev. neurol. **2**:646 (Nov.) 1931.

Instead of injecting 25 per cent sodium iodide into the carotid artery, a procedure that often gave rise to epileptiform seizures and transient hemiplegia as well as to some distress to the patients, the authors have given colloidal thorium dioxide preparation to delineate the arterial tree in the brain. This is given by direct injection into the common carotid artery, the films being taken during the injection. According to the authors, there is no disagreeable sensation. Several exposures may be made, and the opaque medium furnishes a better contrast than sodium iodide. Injections may be made into one carotid artery after the other.

FREEMAN, Washington, D. C.

AN ABNORMAL TYPE OF RETINAL ARTERIAL PRESSURE IN INTRACRANIAL HYPERTENSION DUE TO A TUMOR. G. WORMS and G. CHAMS, Ann. d'ocul. **168**:749 (Sept.) 1931.

A case is reported by Worms and Chams in which there was increased intracranial pressure, probably due to a tumor, and in which the diastolic retinal blood pressure was from 10 to 15 mm. lower than normal. The hypotension preceded the appearance of papilledema by three months. Whereas it is usual to find disproportionate increase in the retinal diastolic pressure as compared with the brachial diastolic pressure in patients with increased intracranial pressure, the usual picture was reversed in the case reported.

THE EFFECT OF STRYCHNINE ON THE OCULAR REFLEXES. KYRIELEIS, Ann. d'ocul. **168**:765 (Sept.) 1931.

The effect of strychnine on the ocular reflexes has been studied by Kyrieleis. Subcutaneous injections of strychnine produced the following changes in the ocular reflexes: The iris reflex to light was jerky at first, and the maximum contraction was attained more rapidly. This observation was proved with the moving picture camera. The latent period of caloric nystagmus was reduced 44 per cent. The time for complete dark adaptation was shortened, but the maximum sensitivity to light was not increased.

A SINGULAR CASE OF OPHTHALMIC MIGRAINE. M. E. HERBERT, Ann. d'ocul. **168**:840 (Oct.) 1931.

Following the ingestion of methenamine Herbert experienced ophthalmic migraine which commenced with bilateral central scotomas and was followed by bilateral hemianopia, more marked on the left side. He inquires whether certain cases of ophthalmic migraine may not be attributed to drugs which, through their toxic action, cause angiospasm.

A BENIGN FORM OF GRADENIGO'S SYNDROME. R. GAILLARD-BUJADOUX and GUICHARD, Ann. d'ocul. **168**:750 (Sept.) 1931.

Gaillard-Bujadoux and Guichard observed a benign form of Gradenigo's syndrome in a girl, 18 years of age. Complete paralysis of the external rectus was noted in the course of erysipelas and acute otitis media. The roentgenograms were positive, and antrotomy was performed. The paralysis of the sixth nerve improved rapidly following this operation.

QUININE AMAUROSIS. M. J. CHARAMIS, Ann. d'ocul. **168**:748 (Sept.) 1931.

Charamis saw a patient with quinine amblyopia who was apparently benefited by large doses of acetylcholine, amyl nitrite and glyceryl trinitrate. The visual acuity improved to 0.9 and the fields were practically normal, but the optic disks remained pale and the vessels were contracted.

BINASAL HEMIANOPIA IN TUMORS OF THE HYPOPHYSEAL REGION. J. A. CHARAMIS, Ann. d'ocul. **168**:737 (Sept.) 1931.

The subject of binasal hemianopia in tumors of the hypophysis has been studied by Charamis. He observed a patient who had a suprasellar tumor. This caused intracranial hypertension, papilledema and binasal hemianopia. Deep roentgenotherapy improved the visual fields.

BERENS, New York.

Society Transactions

PHILADELPHIA NEUROLOGICAL SOCIETY

Regular Meeting, Jan. 22, 1932

JOSEPH MCIVER, M.D., *President, in the Chair*

A CASE OF JUVENILE FAMILIAL AMAUROTIC IDIOCY. DR. A. M. ORNSTEEN.

This article will be published in full elsewhere.

AN UNUSUAL CASE OF EXTRAPYRAMIDAL SYNDROME. DR. LYLE LANYON.

The patient, a white man, aged 30, was admitted to the wards of the Philadelphia General Hospital in June, 1930. After study, the case was diagnosed as one of Wilson's disease. While Dr. Winkelman was on service, the case was reviewed, and a number of findings were found to be incompatible with the established diagnosis. The findings at this examination and a fuller detailed history from the mother of the patient yielded the following:

The patient was born on April 17, 1901. Birth was natural, no instrument being used, but he was a "blue baby." Labor lasted twelve hours; he was the mother's first child. The patient was breast fed. During the first year pneumonia developed, and within the next few years the patient suffered from measles and pertussis. The patient began to walk at the age of 18 months, but stumbled with the left leg over any slight elevation in the path. This condition became so pronounced at the age of 3, that the patient was taken to the clinic at the Orthopedic Hospital. Here the mother was told that the child was in no need of a brace, and that they thought he would outgrow the difficulty. At the age of 6, intention tremors of both arms and the left leg developed. The boy began school at this time. He got along well in school, but at 12 he was unable to write with a pen because of tremor. Schooling was stopped at the age of 15, when he finished grammar school. Within the next two years his voice gradually became hoarser; a catch in it was noticed at times. The boy was taken to a physician, who recommended the removal of the patient's tonsils and adenoids. This was done, but without effect on the condition of the throat. At the age of 20, it was difficult to understand the patient, and within the following five years the condition progressed so far that even the mother was unable to understand him. About this time the patient complained of a sensation as though his jaws were locking when he chewed food. When he reached the age of 29, his general condition was so bad that the family physician recommended hospitalization.

A thorough search through the family history failed to reveal a similar condition in any of the relatives. Two of the mother's sisters had had St. Vitus' dance when young, and one of these had died of a mitral disease.

Physical examination showed intention tremors of the jaw, arms and legs. The teeth were in poor condition, and the patient complained of some tenderness around the umbilicus when this region was palpated.

Neurologic examination revealed: intention tremors of all extremities; twitchings of the face, eyelids and abdomen; a peculiar shuffling gait, the left leg being thrown out and around somewhat as in hemiplegia; marked finger-to-nose ataxia, with little or no heel-to-knee ataxia; slight dysmetria and adiadokokinesis in the arms; a coarse tremor of the tongue and an anarthria. Laboratory examinations all gave negative results.

The facts reported seemed to indicate that the established diagnosis required modification. Wilson's disease was ruled out by the absence of (1) a parkinsonian syndrome with cirrhosis of the liver; (2) nonintention tremors; (3) rigid,

hypertonic musculature; (4) contractures, and (5) by the fact that the span of life in this disease is from four months to seven years. Pseudosclerosis of Westphal was ruled out by the absence of: (1) marked dementia; (2) slow intention tremor; (3) hemiparesis and apoplectiform or epileptiform attacks, and (4) contractures. The diagnosis thought most likely was cerebral diplegia with athetosis. This was entertained for a number of reasons: (1) the patient being a first born child, with asphyxia neonatorum, (2) the early onset of locomotor disturbance, with development of a shuffling gait, and (3) progressive bulbar involvement. The pathologic changes in this case fit in with the *"état marbré"* of Cécile Vogt.

DISCUSSION

DR. N. W. WINKELMAN: This patient presents a very unusual picture. Several facts were not brought out clearly. The boy was the first born and was asphyxiated at birth—two common facts in the history of cases of cerebral diplegia or what is popularly called Little's disease. The gait is characteristic of this condition. He shows also a peculiar athetoid type of movement of the musculature concerned in talking and swallowing, which makes it extremely difficult for him to talk or eat. This conclusion is arrived at because the movements cease completely during sleep and occur only on attempts at active movement; they are irregular and bizarre in character, and are hypertonic in nature. We have interpreted the condition as being a bulbar form of athetosis occurring in a cerebral diplegia, similar to the cases described by Oppenheim and others.

DR. JOSEPH C. YASKIN: At the present time, at the Graduate Hospital, there is a girl, aged 13 years, who presents symptoms very like those in this case; they began at the age of 5 months. In her case, too, the involuntary movements become more pronounced when she attempts to move or to talk. As in the patient presented here, there is a considerable cerebellar component, but an encephalogram failed to disclose any features of importance. We therefore concluded that the pathologic condition in our case was in the corpus striatum and to some extent in the cerebellar pathways.

DR. WILLIAM G. SPILLER: I cannot accept the statement that athetoid movements never occur except on voluntary movement. This is true in certain cases, but there are other cases of athetosis in which athetoid movements occur at times without any apparent voluntary movement. Voluntary movements usually increase athetoid movements, but the latter may be observed in certain cases of athetosis as the result of excitement or psychic disturbance, and may occur when the patient is brought before an audience.

DR. N. W. WINKELMAN: I am afraid that I cannot entirely agree with Dr. Spiller that athetosis is present at rest. It is well known that practically all extrapyramidal movements cease during sleep, and athetosis is no exception to this rule. In my studies of athetosis I have been impressed by the fact that when a patient is making no movement at all the athetosis completely disappears, but on the least effort at voluntary movement there begin the peculiar, wormlike movements with hypertonicity that are called athetosis.

UNILATERAL ATHETOSIS WITH ENCEPHALOGRAPHIC FINDINGS. DR. DAVID NATHAN.

The patient I present is of interest because of the difficulty in definitely deciding whether cortical or subcortical structures are the offending part in athetosis and whether both are implicated in any or in all cases. Choreiform, choreo-athetotic and athetotic movements have been the subject of much controversy relative to the parts responsible for their existence.

The patient, aged 24, was well until he was 6 or 8 years of age, when he had scarlet fever. He had most of the diseases of childhood at about the same time, and states that while ill he fell out of bed. Following this illness a weakness of the left side developed. There is no other history obtainable. He had influenza at the age of 18. Tenotomies were performed on two occasions—on the sole of the left foot and on the left tendo achillis—with indifferent results.

Mentally, he appears alert and presents an intelligence quotient that is equal to the opportunities and environment that have been his.

On neurologic examination he presents paresis of the left arm and left leg, associated with marked spasticity, and athetoid movements of the left arm, hand, left leg and left foot. There is general atrophy of the left arm and leg. The cranial nerves are intact. The biceps and triceps jerks are hard to elicit on the left, but are exaggerated. The knee and achilles jerks are also exaggerated on the left. Hoffman's sign cannot be made out. A Babinski sign is present on the left. The left abdominal reflexes are absent. No sphincter disturbance is present. Sensation in all its modalities appears undisturbed. There is no astereognosis. There are no cerebellar disturbances.

The condition is therefore one of infantile cerebral hemiplegia associated with athetosis.

Encephalographic studies, made in December, 1931, showed a diffuse bilateral cerebral atrophy involving both frontal lobes and extending to the precentral area. There was slight generalized atrophy in the postrolandic area near the vertex. In the inferior and anterior portions of the left parietal lobe there was a large central defect anterior to the thalamus on the right and extending toward the island of Reil. This sharp loss of brain mass lay in the region of the internal capsule and the anterior portion of the striate area. The cisterna venae magnae cerebri was enlarged, the cerebellar folia were visualized on the superior surface, and the basal cisternae were slightly enlarged. The ventricles were approximately normal in size and, aside from the defect in the right anterior horn, apparently normal in shape.

The impression was of diffuse degenerative cerebral atrophy, bilateral frontal, with subcortical degeneration on the right.

DISCUSSION

DR. N. W. WINKELMAN: It is recognized that athetosis occurs practically always in association with hypertonicity of the musculature. As far as I know, one case has been reported in the German literature, which occurred after an acute attack of epidemic encephalitis that began in adult life. I have never seen athetosis except as the result of a lesion occurring in earliest infancy. The Vogts have stated their belief that athetosis is an inborn condition of the brain. I was curious to see whether S. A. K. Wilson's assumption that the cortex probably takes an active part in the production of involuntary movements could be demonstrated during life. For this reason an encephalographic study was done by Dr. Fay. We were greatly surprised to find a cortical atrophy of rather intense degree, but equal on the two sides, even though the athetosis in this boy is unilateral. Cortical atrophy probably accounts for the mental enfeeblement.

DR. A. M. ORNSTEEN: The assertion that athetosis cannot be acquired in adult life is rather sweeping. It is true that the ordinary conception of athetosis has reference to congenital disorders and that its occurrence in acquired lesions may be infrequent. The statement brings to mind an athetoid condition in the form of "mobile spasm" in von Bechterew's hemihypertonia postapoplectica. No one can question the athetoid character of the spasm in this condition, and if an acquired lesion can produce a focal athetoid manifestation, then it is not impossible for a more widespread lesion in adult life to produce a picture more typical of the general type of athetosis. In chronic encephalitic states one occasionally observes athetosis involving the facial, cervical and bulbar muscles.

I do not agree that athetosis occurs only at rest. It is a common experience to observe patients with athetosis continually squirming in their chairs or in bed when no voluntary activity is intended. It is conceded that these movements are intensified by volition and by emotional influences. There are cases of athetosis in which the movements may be initiated by volitional activity, but it cannot be said that athetotic patients have no spontaneous movements. With the aid of slow motion pictures of such cases I have been convinced of these facts.

DR. DAVID NATHAN: I can conceive of the patient being still and not presenting athetotic movements. If the patient is quiet and in a psychic state not calling forth involuntary movements, as during sleep, then certainly there is no athetosis.

THE SEQUELAE TO HEAD INJURIES. DR. JOSEPH MCIVER.

Dr. McIver's presidential address will be published in full elsewhere.

Regular Meeting, Feb. 26, 1932

A. M. ORNSTEEN, M.D., *President, in the Chair*

A CASE OF PROGRESSIVE DEGENERATIVE SUBCORTICAL ENCEPHALOPATHY (SCHILDER'S DISEASE). DR. J. C. YASKIN, DR. B. J. ALPERS and DR. C. A. PATTEN.

The real reason for presenting this case is to obtain help in diagnosis. The title of progressive degenerative subcortical encephalopathy was forced on us by exclusion of other possibilities rather than by any direct clinical evidence.

REPORT OF CASE

Headache and left-sided jacksonian convulsions followed by a left hemiparesis subsequent to a crop of boils. Craniotomy failed to reveal any pathologic condition. Ten weeks later, spastic paralysis of the right leg with secondary optic atrophy, tremor of the left arm and leg, and definite mental impairment.

History.—J. W., a boy, aged 9, was admitted to the Graduate Hospital (service of Dr. T. H. Weisenburg) on Dec. 14, 1931, with weakness of both the lower and the left upper extremities. He was the fifth of seven children, and was born at full term; delivery was rapid with the aid of a midwife. He sat up at 5 months, walked at 1 year, talked at about 1 year and gained control of the sphincters at about 1½ years. Although the father stammered, the child is said never to have stammered until the onset of the present illness. Except for measles, he had had no serious illness, injury or operation. He is said to have been somewhat backward and nervous, and for that reason did not start in school until the age of 7; he had to repeat at least one grade.

The patient was in good health until the end of August, 1931, when he had boils around the buttocks, which were treated by the mother. On the third Tuesday in September, a severe headache suddenly developed which was relieved by the administration of a headache powder. The patient was well on the following day but on Thursday had another severe headache, which was followed by vomiting, convulsions on the left side of the body and, finally, loss of consciousness. This condition was relieved by an enema. On the following day there was paralysis of the left arm and leg, and on September 26, the patient was admitted to the Presbyterian Hospital. On October 13, craniotomy was performed on the right side, but no evidence of an abscess or any other space-taking lesion was discovered. The patient made a satisfactory surgical recovery and was discharged on December 3, with paralysis of the left arm and leg, slight tremor of the left arm, and ability to walk without assistance. On about December 10, he accidentally fell while walking; shortly thereafter paralysis in both lower extremities was observed, and he was admitted to the Graduate Hospital.

Physical Examination.—The child was poorly nourished and rather pale, but apart from evidences of sinusitis and chronic tonsillitis, physical examination gave essentially normal results.

Neurologic Examination.—The child lay on the flat of his back, with his head turned sharply to the right. The left forearm was sharply flexed on the arm, and

the fist was clenched. There was a continuous coarse tremor of the left hand. An attempt to straighten the head caused turning of the eyes sharply to the right. The legs were fully extended and had a tendency to cross each other. They were so rigid that the whole body could be lifted by pulling on the heels. There was no rigidity of the neck.

The disks were small; the margins, oval; there was light infiltration of the cup. The whole disk was of a yellowish tinge. The ophthalmologic diagnosis was that of a secondary optic nerve atrophy which was more marked on the right than on the left. Perimetric studies could not be carried out. The left pupil was slightly larger than the right, but both responded well to light and in accommodation. There was slight weakness of the left lower part of the face, which was more pronounced on voluntary than on emotional innervation. He stammered from time to time in the course of the examination. There was pronounced trunkal weakness, and the patient was totally unable to arise to a sitting position. The left abdominal reflex was absent; the right was preserved.

The right upper extremity presented no weakness. The tendon reflexes were increased, and there was a Hoffman sign. The left upper extremity was sharply adducted at the shoulder, and flexed at the elbow and at the fist. It was paretic throughout; any attempt to carry out either a voluntary or a passive motion resulted in a coarse rhythmic tremor, which disappeared when the arm was put to rest. There was pronounced increase of tone and marked increase of the biceps and triceps reflexes. Both lower extremities were extended and rigid; they crossed each other. There was almost complete loss of voluntary innervation. The knee and achilles jerks were bilaterally exaggerated, and there was a Babinski sign bilaterally. The child responded normally to pin-prick stimulation all over the body, but other tests for sensation or synergy were impossible. There was incontinence of urine and feces.

Mentally, the boy was sluggish, showing a considerable mental defect for a boy of his age. This was especially pronounced in attempting to carry out simple commands.

Laboratory Data.—There was a slight elevation in temperature averaging 99 and 99½ throughout his residence in the hospital. Repeated examinations of the urine, complete blood counts and studies of blood chemistry gave normal results. The Wassermann reaction of the blood was negative; the spinal fluid was under normal pressure and was normal in every respect. A roentgen examination made on December 19, revealed evidences of a craniotomy but no other pathologic findings. Encephalographic studies made on December 27 (Dr. F. C. Grant) revealed no abnormalities excepting slight distention of the cisterna chiasmatis and deviation of the third ventricle and right lateral sinus to the right. This was accounted for by the craniotomy and resultant decompression. A psychometric examination, made on Jan. 28, 1932, gave the mental age as 5 years, 10 months; the psychologist thought that there had been considerable intellectual loss since the onset of the illness.

Course.—During the residence in the hospital, the general physical condition improved markedly. The neurologic status, on the other hand, showed few, if any, changes. The conjugate deviation of the head to the right disappeared, and gradually the head become turned to the left. There also appeared a rhythmic coarse tremor of the entire left lower extremity but none of the right lower extremity. It was noted that the right upper extremity was becoming rigid at the shoulder joint. An examination on February 23 revealed definite mental impairment. There were: secondary optic atrophy, weakness of the left lower part of the face and occasional stammering but no other speech difficulties. There was no rigidity of the neck; the head was kept turned to the left; the patient was unable to sit up without assistance and fell back on removal of the support. The abdominal reflexes were abolished; the cremasteric reflexes were feeble. The right arm showed increased tone and some limitation of voluntary innervation at the shoulder. The left upper extremity and both lower extremities were as on admission, excepting for a coarse tremor which had developed in the last few

weeks. Most of the time the patient was incontinent. He appreciated accurately pain, touch, position and vibration.

Comment.—The disease process was of acute onset and progressive, and involved the white matter of the cerebrum; it was accompanied by optic atrophy without evidence of increased intracranial pressure, and was associated with mental impairment. Therefore, it falls into the miscellaneous group of cerebral involvement designated as encephalitis or the encelelopathies, in which there is a demyelinization of the subcortical white substance with little or no cortical involvement. Chief among these is Schilder's disease. A broader classification is suggested by the term of progressive degenerative subcortical encephalopathy of Globus and Strauss (Globus, J. H., and Strauss, L.: ARCH. NEUROL. & PSYCHIAT. **20**:1190 [Dec.] 1928); these authors regarded the process as purely degenerative. This appears to be the consensus of most neuropathologists. It is also agreed that the process is toxic in origin, and that no definite etiology is known. In this connection it may be of interest to note that the onset of symptoms in this case was preceded by a crop of boils. It is also worthy of note that epilepsia partialis continua has not been recorded in any of the twenty-six cases reviewed by Globus and Strauss.

INVOLUNTARY MOVEMENTS OF THE HEAD. DR. ALFRED GORDON.

Spasmus nutans in very young children is not frequent, especially in favorable surroundings. In the majority of cases nystagmus is associated with it. The case on which this study is based presents some instructive features in this respect and in the physiology of muscular coordinations.

In a girl, aged 8 months, rotary movements of the eyes developed at the age of 5 months. No acute illness preceded the condition of the eyes. One month after the optic symptoms, oscillations of the head appeared. These are fine, very rapid and rhythmic; their amplitude and frequency resemble those of the eyes. The movements of the head ceases when the child's attention is attracted or when the head is leaning against an object. The nystagmus is constant, irrespective of the position of the head. Further somatic examination gives entirely negative results. The reflexes, sensations, motor power, pupillary reactions, eyegrounds and musculature are all normal. There is no external evidence of rickets. Intelligence is normal.

Comment.—The nystagmus presents some peculiarities. In horizontal nystagmus of other conditions the anteroposterior axes of the eyes usually remain parallel. This is not so in this case. Sometimes the nystagmus of one is rotatory and of the other horizontal.

The association of nystagmus with spasmus nutans cannot be considered a mere coincidence if one bears in mind the similarity in character of the movements of the head and the oscillations of the eyes. The syndrome in question usually develops during the first few months of extra-uterine life, when the infant gradually learns coordination of movements of the eyes and head.

In normal conditions the movements of the head follow those of the eyes. They are naturally of a conjugate type. When the movements of the eyes are disturbed, especially when the aforementioned types of nystagmus make their appearance, the child acquires a purposive way of oscillating the head in order to follow the eyes. In this pathologic process there is at first loss of voluntary control of the extrinsic muscles of the eyes and then failure to establish voluntary control of the head as a consequence. Spasmus nutans is the result.

As to the etiologic factors in the loss of voluntary control of the muscles of the eyes, prolonged exposure to poor lighting has been considered. In the case described here this factor is conspicuous. The room of the child is gloomy, dark in the daytime and poorly lighted at night. However, some observers are opposed to this view.

The entire clinical picture of spasmus nutans may be considered as a functional abnormality or as a defective power of coordination in the muscles of the eyes and

in those of the neck. Since there is no underlying etiologic factor of an organic nature, the prognosis should be considered favorable.

In the therapeutic management of such cases special attention should be given toward avoiding conditions in which the muscles of the eyes are compelled to function under tension. The latter is possible only when the patient is placed in continuously sufficient light. Since the oscillations of the head are intimately connected with nystagmus of the eyes, improvement in the condition of the latter will be followed by amelioration and disappearance of the abnormal movements of the head. Recovery usually occurs within a few months.

TUMORS OF THE GASSERIAN GANGLION. DR. MELBOURN COOPER.

This paper is to be published in full elsewhere.

FOCAL ENLARGEMENT OF THE TEMPORAL BONE AS A SIGN OF TUMOR OF THE BRAIN. DR. ROSS H. THOMPSON.

This paper is to be published in full elsewhere.

FIVE CASES OF MARIE'S CEREBELLAR ATAXIA. DR. GEORGE WILSON and DR. MURRAY FRIEDMAN.

Marie's hereditary cerebellar ataxia is considered to be a primary parenchymatous degeneration of the cerebellum. It is closely related to Friedreich's ataxia, in which degeneration of the posterolateral columns leading to the cerebellum occurs. However, there is no loss of knee jerks or affection of the plantar reflexes in Marie's ataxia; scoliosis and pes cavus do not occur and the age of onset is somewhat later. Optic atrophy, which does not occur in Friedreich's ataxia, is fairly common in Marie's ataxia, although this is not seen in any of our cases. An intention tremor and ocular palsies, such as ptosis and strabismus, have been described in this condition. The disease progresses slowly, usually without remission.

Five cases that seem to fall into this category are presented. A sixth case with a picture closely resembling Marie's ataxia is shown with this group.

Cases 1 and 2 (S. H. and C. H.).—These cases are remarkable in that the patients are identical twins. Their histories are exactly parallel, except that in the patient in case 2 an irascible and quarrelsome disposition developed while his brother remained quiet and cooperative. The onset of the illness is dated in 1908, at the age of 34, when both began to suffer increasing difficulty in walking. Shortly afterward it was noticed that speech was thick and indistinct. The patients were admitted to the hospital in 1919. The Romberg sign was positive. Adiadokokinesis was marked. There was an intention tremor. The knee and ankle jerks were normal, and the Babinski sign was uncertain. Examination of the eyes revealed nystagmoid movements on extreme lateral rotation. The disks were well defined but of a dirty gray. An encephalogram in case 1 suggested some convolutional atrophy of the frontal lobe. Serologic tests were negative.

Case 3 (H. E.).—The patient was kindly loaned to us from the service of Dr. McConnell; he was admitted to the hospital in 1926. He had been perfectly well until 1920, when he fell on his back and was unconscious for one hour. Following this, he was never quite well and complained of increasing vertigo and headache. In 1925, he was forced to give up his job because he was unable to walk without staggering. In 1926, he had transient diplopia, and noticed that he was having difficulty in speech. Examination on admission revealed severe diplopia, horizontal nystagmus and slurring speech. He had a marked intention tremor. The Babinski sign was absent. The abdominal reflexes were intact; the deep tendon reflexes were uniformly and moderately exaggerated. Ankle clonus was demonstrated on both sides. Examination of the fundi gave negative results. Serologic tests were negative. Four siblings in this family are similarly affected. One of them, a sister, has been examined by Dr. Patten, and the case was diagnosed as hereditary cerebellar ataxia.

Case 4.—The onset of the illness, in 1923, in A. B., aged 57, was gradual, coming on with an awkward gait which grew steadily worse. In 1928, diplopia, vertigo and severe frontal headache developed. He was admitted in October, 1928. On examination he was found to have a markedly ataxic gait, walking on a wide base and swaying from side to side. The Romberg sign was positive. The pupils were slightly dilated and reacted sluggishly to light and in accommodation. There was slight ptosis of the left eye, but no nystagmus. The disks were gray, particularly on the temporal sides. There was a suggested intention tremor. The deep tendon reflexes were normal. There was a mild adiadokokinesis. An encephalogram gave negative results.

Case 5.—J. S., aged 38, was admitted on Sept. 22, 1930, complaining of weakness, staggering and pains in the back and legs. The symptoms had begun in 1925 and grew worse gradually. He grew quite ataxic and, shortly after the onset, increasing vertigo and pain in the back and legs appeared. Speech became thick, and he found that he was having difficulty in pronouncing some words. On examination he was found to have lateral nystagmoid movements on extreme lateral rotation. He was ataxic; the finger-to-nose test was poorly performed, and adiadokokinesis was pronounced. All the deep reflexes were exaggerated. The plantar reflexes were normal. The abdominal reflexes were not obtained. Serologic tests were negative.

Case 6.—The onset of illness in H. A., aged 52, was in 1915 after a fall on the back which disabled him and prevented him from working for three years. He suffered dull aching pain in the lumbar region and, about eight months following the accident, began to experience difficulty in walking and in using his hands. At times he was incontinent. On examination he was found to have no nystagmus. The gait was ataxic; the Romberg sign was positive, and the deep tendon reflexes were exaggerated. Speech was thick and slow, and a transitory drooping of the left upper eyelid was noticed. Adiadokokinesis was demonstrable; Babinski's sign was absent, and the abdominal reflexes were present. This patient manifests cerebellar symptoms. The absence of nystagmus, and the normal abdominal and plantar reflexes point away from multiple sclerosis. While in some respects the condition conforms to Marie's cerebellar ataxia, the history of injury preceding the symptoms cannot be ignored as an etiologic factor.

DISCUSSION

DR. FREDERIC A. LEAVITT: Dr. Wilson's presentation of identical twins developing cerebellar ataxia at the same time is of great interest to me. Has a study been made of the whorl patterns of their palms and soles? (Answer: "No.") Some time ago, I presented before this society identical twins exhibiting epilepsy occurring at the same age and other patients with manic depressive psychosis developing at the same time (although the twins were far removed from one another at the time of their mental condition) and patients with cerebellar tumors of the vermis developing in identical twins at the same time. Dr. Wilson's presentation of these twins adds further data to the pathogenesis of organic nervous diseases.

NEW YORK NEUROLOGICAL SOCIETY

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S. PHILIP GOODHART, M.D., *President, in the Chair*

MYASTHENIC REACTION (JOLLY) IN FRIEDREICH'S DISEASE (MYOGRAPHIC STUDY: LANTERN SLIDES). DR. PETER MAYBARDUK.

A number of cases on record show the occasional occurrence of the so-called "myasthenic" or "Jolly" reaction in conditions other than myasthenia gravis. The reaction is by no means a constant sign in myasthenia gravis itself. Stripped of

its pathognomonic value, the myasthenic reaction of Jolly is, nevertheless, still considered a characteristic symptom of the aforementioned disease only. In view of this, it is of interest to report a series of cases of Friedreich's disease in which a careful investigation of electrical excitability of the muscles revealed Jolly's reaction in each case. The series comprised all available cases (eight) of the disease in the wards of the Neurological Hospital during the years 1926 to 1932.

Absence of deep reflexes, marked hypotonia in all extremities, muscular atrophy, impairment of coordination, sensory changes, presence of specific cerebellar signs (Gordon Holmes phenomenon, decomposition of movement, spontaneous deviation, adiadokokinesis, and the like) and skeletal deformities (such as pes cavus, "hammer" toe, scoliosis, kyphosis)—the typical components of Friedreich's disease—were found in each case of the series. Laboratory examinations revealed nothing of significance. Roentgen examination of the chest in five cases showed no thymic shadow.

Electric Examination of the Muscles.—Atrophy of the muscles, which was present in all these cases, suggested an electric examination. The primary purpose of the examination was to determine whether or not the so-called "reaction of degeneration" was present. Therefore, at first only those muscles which seemed to be atrophic were tested. The reactions obtained were confusing. It was observed, first, that the strength of the current (faradic or galvanic) required to produce the weakest contraction varied in the same muscle when tested at different times; secondly, that certain muscles also exhibited a variability in speed of contraction; thirdly, that occasionally an anodal closure contraction response could be obtained at times in muscles with a weaker current than cathodal closure contraction, and at other times, in the same muscle, the reverse was true. At this stage of the investigation it was difficult to reach any definite conclusion as to the significance of these peculiarities.

On further investigation still another phenomenon was observed: An attempt to find the minimal effective stimulus by gradually decreasing the strength of the current terminated at times in abrupt cessation of response, in spite of the fact that the last contraction was still extremely forceful. This observation first led me to suspect that I was dealing with the myasthenic reaction of Jolly. Indeed, with the appropriate method of stimulation, which will be described, I found little difficulty henceforth in detecting this reaction in various muscles in every case of the series. The failure to obtain similar results in the earlier tests was obviously due to the fact that the only method used was that designed to detect the reaction of degeneration; this method, as is known, requires the application of varying strengths of current, while in Jolly's reaction short, tetanizing, faradic stimuli of equal strength, repeated at regular intervals of about a second, are usually applied.

Thus stimulated, a muscle would show a gradual diminution in intensity of contractions, the latter finally disappearing completely, but after a short rest of one to two minutes the contractions would reappear with their original intensity.

Continuous application of faradic current produced at times an effect similar to that seen during the application of intermittent stimulation; more often, however, the following phenomenon was observed: During continuous stimulation a muscle at first would behave normally; e. g., it would respond with a seemingly continuous contraction (tetanus), but after a short period the contraction would break up into a series of clonic contractions resembling a tremor. In some instances the clonus would appear with the onset of stimulation. (This failure of the implicated muscle to fuse successive contractions I designate as the "breaking up" phenomenon.) Fibrillary contractions were often observed in response to both intermittent and continuous stimulation.

It is interesting to note that after the muscle no longer responded to faradic stimulation, it would almost invariably respond to galvanism.

The effect of indirect stimulation was also investigated. I chose for this the peroneal nerve. The myasthenic reaction was found in most of the cases, though it was not so marked as during direct stimulation.

During the investigation I occasionally met with a phenomenon similar to that designated by Rautenberg as "myautonomy": A muscle on intermittent faradic stimulation would suddenly fail to respond for a short period, though a few stimuli were still applied; in a few seconds, however, delayed contractions would appear without the stimulation being continued. Another phenomenon described by the same writer was frequently observed: "myobradia," or increasing sluggishness of contractions on protracted stimulation.

Jolly's reaction was found not only in the muscles affected by amyotrophy but also in those with an apparently normal bulk. It is not possible to draw definite conclusions as to the effect of amyotrophy on the myasthenic reaction because of the great variability of the latter; it is not always marked to the same degree in the same muscle, and in some instances it is not present at all times in a given muscle. Still, I am under the impression that atrophied muscles showed a more rapid failure of response and weaker contractions than apparently normal muscles.

In two patients all accessible muscles were tested, including the muscles of the face, and after repeated tests Jolly's reaction was found in almost all of them. In the remaining patients only the following muscles were investigated: the biceps, the triceps, the thenar and hypothenar groups, the interossei, the quadriceps and gastrocnemius groups and the muscles of the face. The reaction was seen in all these muscles in each case, though not invariably.

Myographic Examination.—Five of the eight cases were studied myographically.

Method: An interrupter to make and break the current and a small electromagnet armed with a pointed lever to mark the beginning and end of each electric stimulation on a kymograph were interposed in the primary circuit of a faradic machine. To the two binding posts of the secondary coil were connected a pair of electrodes, which served to excite muscular contractions. The graphic record of muscular reactions was obtained by means of a pneumograph connected by a rubber tube to a Marey's tambour. (The use of the pneumograph was suggested to me by Dr. Dayton J. Edwards of the Cornell Medical School.) At the closure of the interrupter the current was set up both in the primary and in the secondary circuits, thus producing a practically synchronous activation of the two writing levers — that of the electromagnet and that of Marey's tambour. This arrangement of the apparatus made it possible to obtain a simultaneous record of each stimulation and its resulting reaction.

When the muscle to be tested was so small as to make the use of the pneumograph impracticable, as, for instance, when testing the interossei, the reaction was recorded by means of an ordinary writing lever attached by a string to the part moved on stimulation of the muscles.

The mode of stimulation was the same as that used in the electric tests.

Kymographic Records: Each record obtained by this method shows two parallel tracings, the graphic record of stimulation (signal tracing) and that of muscular response (reaction curve). In some records the signal tracing shows division into zones separated by straight lines, under which the word "pause" appears. Such a zone represents one stimulation cycle. Since the stimulation and its effects were recorded simultaneously, the reaction curve also shows division into zones corresponding to those of the signal tracing. Each wave in a reaction curve represents a single muscular contraction produced by a short, tetanizing, faradic stimulus. A zone in a reaction curve is thus a graphic record of muscular response to a series of faradic stimulations.

Various muscles in each of the five cases myographically studied yielded similar curves when tested for myasthenic reaction: the amplitude of successive waves within a zone diminishes with each stimulation, and finally the wavy character of the curve disappears completely, being changed into a straight line indicating that the muscle has lost its excitability. But with the renewal of stimulation after a short pause (varying from one-half to two minutes), the curve assumes its original form. Such a tracing thus reveals the typical characteristics of the myasthenic reaction of Jolly: rapid failure of muscular response on electric

stimulation and reappearance of contractions after a short pause. It is interesting to note that at times the muscle shows a tendency to recover its excitability in spite of protracted stimulation. This apparently takes place during the refractory period (Steinert's phenomenon). Some of the curves show myobradic (sluggish) contractions, which usually yield waves of unequal amplitude and of irregular form.

A series of tracings shows the effect of the strength of the current on the myasthenic reaction. When a moderately strong current is applied, the myasthenic phenomenon appears earlier than it does when the same muscle is stimulated with a stronger current. Moreover, the application of an extremely strong current often fails to show any diminution of response within a stimulation period much longer than that usually sufficient to induce complete cessation of contractions.

The effect of indirect stimulation has already been pointed out; the kymographic records did not reveal additional features.

The "breaking up" phenomenon elicited by continuous stimulation was also studied myographically; a tracing illustrating this phenomenon shows a series of consecutive waves, which lack uniformity in amplitude and form. A striking resemblance is seen between this record and a tremogram obtained by Neustaedter's method from a finger in a case of Friedreich's disease. The only difference between a spontaneous tremor shown in the tremogram and the tremor-like contractions artificially induced by continuous faradic stimulation is a quantitative one: the former is finer than the latter. The spontaneous tremor reveals the same tendency to sudden cessation and rapid reappearance and the same irregular oscillations.

A suggestion of the same phenomenon can be seen in some tracings illustrating the effect of intermittent stimulation; here and there, an individual contraction wave obtained on the application of a tetanic stimulus of short duration shows a jagged contour.

In my opinion this "breaking up" phenomenon constitutes one of the characteristic features of electric excitability of the muscle in Friedreich's disease.

Comment.—Reports of the occurrence of the myasthenic reaction of Jolly in Friedreich's disease are exceedingly scarce. Oppenheim in his textbook cites Kramer, who found in a case of Friedreich's disease the myasthenic reaction more or less marked in all the muscles on faradic stimulation. To my knowledge, this is the only reference of this sort. Even the most recent textbooks on neurology do not include the reaction just named in the symptomatology of Friedreich's disease. The results of my study, however, lead to the conclusion that this reaction is a characteristic feature of electric excitability of the muscles in this disease. It will be recalled that the reaction was found in each of eight cases of Friedreich's disease. This occurrence does not seem to be a mere coincidence, nor can it be assumed that we are dealing with a combination of Friedreich's disease and myasthenia gravis, since in none of the eight cases could the myasthenic phenomenon be elicited on volitional innervation — at least not nearly to the extent seen in myasthenia gravis. The only possible inference is that there is an intimate relationship between the electric myasthenic reaction and the symptomatology of Friedreich's disease. A clinical and physiologic approach bears this out.

The intrinsic clinical features of this disease are asynergia, in its static and kinetic manifestations, and hypotonia. These two allied symptoms are thought to be the chief components of cerebellar symptomatology. It was shown that in each of the eight cases here reported the "cerebellar" symptomatology was well represented (ataxia, dysmetria, adiadokokinesis, asthenia, tremor, rebound phenomenon, and others). This, however, does not necessarily imply a lesion in the cerebellum itself, since symptoms do not always arise at the same physiologic levels. For instance, everyday observation shows that hypotonia may also be produced by interruption of the proprioceptive system in the cord. Furthermore, according to modern neurophysiologic concepts, a symptom can be ascribed to dysfunction at more than one neural level at the same time; for example, a certain "cerebellar" symptom may be caused by a release of a noncerebellar mechanism (e. g., cord) from cerebellar control. Or, in Wilson's words, since "integration

of neural levels is essential to harmonious motor activity, the possibility of disintegration through a series of levels must be steadily borne in mind."

A logical inference from the foregoing statements is that "cerebellar" symptoms may arise from lesions in the cord or in the cerebellum or in both. Clinicoanatomic observations confirm this point. Indeed, Friedreich's disease has widespread anatomic lesions, viz., in peripheral nerves, dorsal and anterior roots, spinocerebellar tracts, pyramidal (?) tracts, the columns of Clarke, the posterior column and at times in the cerebellum itself.

Thus I arrived at the point where Luciani's concept of cerebellar functions as tonic, static and sthenic may be applied to the interpretation of the symptomatology of Friedreich's disease without necessarily implicating the cerebellum in the localization of the mechanism involved. Disturbances in these functions, according to Luciani and Gordon Holmes, may be explained in terms of hypotonia, which as mentioned, is a characteristic symptom of Friedreich's disease.

With Sherrington's concept of tone as postural contraction and Wilson's contention that there is no essential difference between kinetic and static contractions, Jolly's reaction in its various phases may then be interpreted as a succession of changes in posture. In other words, an implicated muscle, stimulated intermittently, responds with a series of alternating kinetic and static contractions and, when stimulated continuously, responds with a seemingly continuous kinetic contraction. The rapid failure of response, however, does not imply disappearance of contraction; what probably takes place is a change from postural (kinetic) tone into plastic (static) tone. The interpretation of Jolly's reaction in terms of tone disorder thus brings out the close alliance between this reaction and the symptomatology of Friedreich's disease, where hypotonia is an outstanding feature.

The explanation of the failure of the muscle to effect or sustain postural contraction becomes the fundamental problem in ascertaining the nature of the myasthenic reaction. In the present state of knowledge, however, no theory advanced in this direction can pretend to be of conclusive value. It may be suggested that the phenomenon of the myasthenic reaction (rapid failure of muscular response on various forms of stimulation) is "physiology in difficulties": the implicated muscle is subjected to adverse physiologic influences. In other words, the problem, as far as the muscle is concerned, is probably a physiologic rather than an anatomic one. This statement seems to find support in the fact that so far no sufficiently constant pathology of the muscles has been found, either in myasthenia gravis or in other neurologic conditions in which the reaction was found.

There is also insufficient evidence to explain the myasthenic reaction on the basis of muscular fatigue in the strict sense. For proof of this statement, I refer to Keschner and Strauss' exhaustive work on myasthenia gravis. As additional evidence, certain facts from my own study may be adduced; Rautenberg's "myautonomy," Steinert's phenomenon and the fact that in the myasthenic reaction the muscle responds well to galvanism after failure to respond to faradism. All seem to reject the theory that "metabolic" fatigue is the cause of the reaction.

Hypotonia, in terms of which Luciani explains the tonic, static and sthenic disturbances, provides a more plausible basis by assuming that the myasthenic reaction is a tone disorder and may be interpreted as a symptomatic manifestation of asthenia. In Luciani's sense, the latter is a muscle weakness resulting from absence of postural tonus.

The "breaking up" phenomenon, the kymographic record of which shows a striking resemblance to a tremogram also obtained from a case of Friedreich's disease, seems to support my interpretation of Jolly's reaction as a disorder of tone and also suggests its relationship to tremor. To quote Wilson: "It does not seem to be a mere coincidence that the levels of the lesions associated with tremor are also those from which alteration of muscle tone in large degree arises." This phenomenon is also important as possibly illustrating the interrelationship between tonic, static and sthenic disturbances, since "a normal, voluntary contraction is 'tetanic'; that is to say, it is a fusion of a succession of individual twitches.

This fusion is aided by the presence of postural tonus, as was shown by Sherrington. In the absence of such tonus, smooth coordinated movements are impossible, because the element for the fusion of separate twitches is lacking. Thus, hypotonia is the cause of astasia. Asthenia and fatigability can also be explained in the same way" (Brain and Strauss).

I am not alone in my interpretation of the electric myasthenic reaction in terms of muscle tone disorder. Keschner and Strauss state that the myasthenic reaction may bear some relation to muscle tone. They admit the possibility that the neural mechanism of tone may reside in the sympathetic nervous system, provided that the theory of dual (motor and sympathetic) innervation of striated muscle is regarded as an established anatomic fact. Furthermore, they think that there is also anatomic and clinical evidence tending to show that in the midbrain, especially in the hypothalamic region, there are higher centers regulating the sympathetic nervous system. If this fact is coupled with the fact that lesions in this region (as observed in epidemic encephalitis) give rise to a syndrome simulating that of myasthenia gravis, then additional evidence is produced in support of the theory that "changes in tonus must be of great significance in the production of the myasthenic reaction."

DISCUSSION

DR. ISRAEL STRAUSS: Some months ago Dr. Maybarduk brought me the tracings that he made in these cases. I think there is no doubt that the tracings show that the myasthenic reaction occurs in Friedreich's disease. When one considers the number of cases, I do not think that one can consider this merely a coincidence. However, the striking point is this: In myasthenia gravis, in which one finds this phenomenon, there is no definite gross or histologic change in the central nervous system. In Friedreich's disease, however, there are definite changes within the central nervous system. One cannot therefore explain the occurrence of the myasthenic reaction in Friedreich's disease on the basis of pathologic changes in the central nervous system, because the same reaction is found in myasthenia gravis, in which there are no such changes. One must, therefore, enter the *terra incognita* in which lies the cause of the myasthenic reaction in myasthenia gravis in order to explain the reaction in Friedreich's disease. I am candid in admitting that I do not know what the underlying cause of the reaction is.

DR. I. S. WECHSLER: Dr. Maybarduk showed me his paper, but, like Dr. Strauss, I was unable to evaluate the fact that he elicited. What interested me was his linking-up of the myasthenic reaction in Friedreich's ataxia with tonus and its interpretation as a cerebellar defect phenomenon. This is in line with Luciani's conception of cerebellar function but at variance with more modern views. However, one fact cannot be easily dismissed. It is known that the frontopontocerebellar pathways are concerned in tonus, since experimental stimulation of these cut fibers overcomes the rigidity in decerebrate animals. It is known also that tonus, according to Sherrington, is a low proprioceptive phenomenon, and that there are suprasegmental structures, namely extrapyramidal basal ganglia, pyramidal and vestibular tracts and red nucleus, which exert a control over tonus. I wonder therefore whether Dr. Maybarduk is justified in speaking of the myasthenic reaction in Friedreich's disease as proof that the cerebellum presides over tonus. Enough is not known about the sympathetic nervous system to define its relationship to tonus. The myasthenic reaction may occur in diseases other than myasthenia gravis and is frequently absent in it. One cannot tell whether the condition is a phenomenon of muscular exhaustion or one that has to do with some disturbance in the neuromuscular junctions. One must know more about nerve-muscle physiology to be able to discuss intelligently what Dr. Maybarduk has shown.

DR. ISRAEL STRAUSS: I wish to ask Dr. Maybarduk, how, if he considers this condition due to disturbance in tonus, he explains the fact that in the many conditions in which tonus is involved one does not obtain the myasthenic reaction. It seems to me that in order to attribute this reaction to disturbance in tonus,

involving either the sympathetic nervous system or the cerebellum, one has to explain why the myasthenic reaction has not been frequently demonstrated in the many conditions in which tonus is lowered.

DR. M. NEUSTAEDTER: I have observed Dr. Maybarduk's work in the Hospital for four years, have carefully watched his cases and can confirm his work. We have had many discussions about tonus. I cannot agree that hypotonia has anything to do with the reaction. I believe that the myasthenic reaction concerns the muscle cell between the two electrodes. Since he has shown a tremograph in a case, I shall mention my experiences. When you take tremograms in Parkinson's disease or multiple sclerosis, diseases in which one encounters hypertonicity, not hypotonicity, the tremogram invariably shows this trend; in about every five or six seconds after ten or twelve waves we find fatigue. That is a typical tremogram in Parkinson's disease. In multiple sclerosis we get a typical tremogram. We should have also a myasthenic reaction as the result of similar fatigue. Yet I have tested hundreds of cases of Parkinson's disease and dozens of cases of multiple sclerosis and have never found a myasthenic reaction. I believe that there is something else involved in cases of myasthenia gravis and am rather inclined to believe that there is a chemical change in the muscle that may be the cause of the condition. In myasthenia gravis, I understand, a great many cases do show cell infiltrations in the musculature which are supposedly thymic metastases. That may produce some chemical change, and there is a possibility of some chemical change going on in the muscle in Friedreich's disease. May I suggest that Dr. Maybarduk continue this work and try to find out what is the cause of the myasthenic reaction?

DR. PETER MAYBARDUK: My assertion that the myasthenic reaction of Jolly belongs to the symptomatology of Friedreich's disease did not seem to meet with objections in the discussion. Some reluctance was shown, however, in accepting my interpretation of the reaction in terms of disorder of muscle tone. This is not surprising, since Dr. Wechsler's statement that there is still uncertainty about the factors underlying tone is, of course, warranted. But to justify my speculation I present the following points: First, I used the concept of tone in the sense in which it was used by such authorities as Sherrington, Holmes and Wilson; second, in linking Jolly's reaction with the symptomatology of Friedreich's disease, I tried to escape the danger of correlating a function with a particular structure; therefore, in speaking of cerebellar symptoms, for instance, I did not implicate the cerebellum as the only possible localization of the lesions concerned. I mentioned the fact, emphasized by Wilson, that a symptom does not always arise at the same physiologic level, and, again, that some symptoms may be caused by dysfunction at more than one neural level.

Dr. Strauss agreed that the occurrence of Jolly's reaction in each case of the series was more than a coincidence; but he wished to know how my interpretation of the reaction accounts for its absence in various conditions in which hypotonia is an essential clinical feature. In reply I may state that the reaction has been seen in such conditions as chronic poliomyelitis, progressive muscular dystrophy and polyneuritis; Kollarits found it in a case of a cerebellar neoplasm; I myself had the opportunity to make a similar observation (a postoperative case). Furthermore, in many conditions in which hypotonia was an outstanding clinical feature Jolly's reaction may have been missed.

Dr. Strauss also asked how to explain the presence of the reaction in myasthenia gravis, a condition without recognizable anatomic lesions in the central nervous system. This highly important question I can answer only in the following way: Jolly's reaction is prone to appear in myasthenia gravis as a result of a defect in the tone-regulating mechanism, whatever the pathologic changes in this disease may be.

This last answer can also be given to Dr. Neustaedter, who advocates the myogenic nature of the reaction, and considers that it may be due to some metabolic changes in the muscle. Regarding the tremograms illustrating postencephalitic parkinsonian tremor, I can only say: The irregularity in range of excursion, in

the form of sudden reduction and cessation of tremor, may be due to various inhibitory factors discussed by Wilson in connection with the same subject. At any rate, these tremograms do not exhibit the phenomenon of the myasthenic reaction.

MICROCINEMATOGRAPHIC STUDIES OF THE EFFECT OF CERTAIN DRUGS ON THE CEREBRAL CIRCULATION. DR. HUBERT S. HOWE.

After years of work on the effects of drugs on the cerebral circulation I concluded that the only accurate method of studying and recording these effects was the employment of moving pictures. I assembled an apparatus whereby motion pictures in color could be obtained. Direct exposure of the cortex through a small trephine opening, with a reflexion of the dura but with the pia-arachnoid left intact, is the method of procedure. I believe that for this particular type of work the direct exposure of the cortex has advantages over the so-called closed window method. The animals were anesthetized with ether by the intratracheal method.

Preliminary reports as to the reaction of the vessels to electric, thermal and chemical stimuli were recorded, as well as the results of intravenous injections of certain drugs.

It was found that the arterioles alone reacted to electric and thermal stimuli. Annular constriction of the arterioles was produced by moderately weak faradic stimuli, while contraction of longer portions of the vessels resulted from stronger electric stimulation. Irrigation of the pia-arachnoid with saline solution of from 38 to 40 C. produced slight dilatation of the arterioles, and moderate constriction resulted from a similar treatment with a saline solution of from 40 to 50 C. Moderately cold solutions (20 C.) produced little reaction, but iced saline solution caused a constriction of the arterial channels.

The local application of a 1 : 100,000 solution of epinephrine produced a marked contraction of the arterioles; this is followed in about two minutes by dilatation, the vessels becoming as large or larger than before the experiment commenced. On the frog's brain the application of epinephrine was always followed by an arterial dilatation. The local application of pituitary produced a moderate but protracted constriction.

One cubic centimeter of 95 per cent alcohol injected directly into the femoral vein produced a slight arterial contraction. This was followed by an increase in the amount of fluid in the subarachnoid space, and occasionally minute spontaneous hemorrhages occurred from some of the smallest vessels. In a few minutes the circulation in the venules became slow, and shortly after this there was also a marked slowing of the circulation in the arterial vessels.

Whenever the rate of circulation is sufficiently diminished, the red blood corpuscles become grouped together in small masses so that the transparent serum is seen between the corpuscular clumps.

The barbital group of sedatives, if injected intravenously or applied locally in a 5 per cent solution, produces slight arterial contraction and an increase in the fluid of the subarachnoid space.

A mixture of amyl nitrite and normal saline solution, if applied locally, produces arterial dilatation.

The local application of a solution of caffeine sodio-benzoate, U. S. P., produces moderate arterial constriction, while intravenous injection is followed by arterial constriction, an increase in the rate of circulation and a fall in the pressure of the cerebrospinal fluid. The intravenous injection of 0.5 Gm. of caffeine sodio-benzoate will cause the cortex of the brain to shrink away from the calvarium if exposed through an open trephine wound.

No definite change in the cerebral vessels is observed following the intravenous injection of hypertonic dextrose solutions.

Foreign particles, such as india ink, bacteria or starch granules, were injected directly into the circulation. These foreign substances were collected into masses by the blood platelets and frequently produced emboli.

DISCUSSION

DR. MICHAEL OSNATO: This work is unique. The greatest bar to the understanding of the chemical changes of living tissue, particularly that of the central nervous system, has been the impossibility of visualizing it.

Until the recent coming of the ultramicroscope one was compelled to be content with the visualization of dead tissue, and thus came the time-honored, ancient, often sterile histologic data supplied by neuropathologists. It seems to me that the old type of investigation has accomplished about as much as it can. All that one can see by fixing agents and so-called vital stains are the coagulants in dead protoplasm; of course, no tissue is stainable until its protoplasm is coagulated. With these methods one sees futile, sterile death, which gives little knowledge of chemical changes during life and extremely little understanding of what goes on biochemically during life in the central nervous system.

The most interesting neuro-histologic studies I have seen were those shown at the American Neurological Association in 1929 by Ludlum and Taft, and I think that their work has received undeserved scant notice. As Dr. Howe said, his work is merely the beginning of what one may easily visualize as a new era in neurohistology and the biochemical study of the living central nervous system.

While the work is epoch-making, it can give but small bits of information at this time, and that only about the vascular elements. The activity of alcohol and barbital in dextrose edema and of the hypertonic solutions and of dextrose in producing dehydration may be explained only in part on the basis of simple osmosis. There is a great deal more involved. There are also disturbances in the arteriovenous pressure and disturbances in the intracranial pressure, but even these are not the entire story, because there must be colloidal chemical changes within the cells themselves, which Dr. Howe's method cannot show. These changes, however, have been visualized by way of the ultramicroscope. In the cell colloids one is dealing with a protein-water system, and the amount of water found in the colloids depends on the nature and the amount of electrolytes dissolved in the media of the cells. That is, the p_H, the hydrogen-ion concentration, the electrolytic concentration, is the all-important factor in deciding whether the protein colloid shall give up or take water. Martin Fisher has shown that the same law governs the complex proteins in this respect as governs the simple proteins, such as gelatin. The absorption of water depends also on the relative affinity of salts and proteins in the colloid mixture for water, and the affinity of protein for water depends in great part at least on the charge imparted by the electrolytes. The effect of the charge on the protein depends in great part on the acidity of the water. This is difficult for neurologists who are steeped in the old-time histology to understand. It seems to me that a great many of the processes in the brain can never be grasped until a good deal more is known about the biochemistry of the central nervous system. If some tremendous ultramicroscopic instrument could be combined with the moving picture studies which Dr. Howe has made, one would see something of the tremendous forces underlying function in living tissues. Recently, Martin Fisher and Hooker have applied these facts to the complex proteins in the brain and spinal cord of rabbits. Ludlum extended the studies to other animals, and showed further that reactions in nerve tissues from either the anion or cation series of salts were usually arranged in the order of the degree of swelling, when this differed by as much as 10 per cent. Under the ultramicroscope the anion series was in this order: sulphate, acetate, chloride and iodide. For the cation series the order was calcium, magnesium, sodium and potassium. That is, these authors were able to distinguish various degrees of hydration of the brain tissue as seen with the ultramicroscope. Of course the method of Ludlum and Taft consisted merely of the removal of bits of living tissue from the central nervous system, pressing them flat with a cover slip, and then examining this still living tissue with the ultramicroscope. How much more one might visualize in the future with a combination of the ultramicroscope and the moving picture apparatus invented by Dr. Howe is a fascinating speculation.

DR. FOSTER KENNEDY: I am gratified to see with the eye those things which for so long have been speculated on by the mind. The presence of angiospasm has been denied by physiologists for a generation. The presence of vasomotor nerves in the cerebral blood vessels has been denied by them, but here we have had the last piece of evidence brought forward. Dr. Howe has shown diapedesis, the changes in the circulation and the edema, all of which many of us have believed for a long time to be responsible for many of the clinical processes that we see. We must compliment Dr. Howe on the excellence of his work.

Dr. Osnato stated that Ludlum and Taft's work was neglected by us all at the American Neurological Association meeting, but at least Wortis and I, after the meeting, went to Philadelphia to spend a day and came away impressed by their work and that of Bancroft; we were confident that here was not only the real proof of the physiology of the brain but a hope of a physiology of the mind. The effect of the study of the living colloids in intoxicated animals, showing dispersal and ability to coagulate, probably will furnish the key to a new psychiatry.

DR. IRVING J. SANDS: I wish to ask Dr. Howe concerning the nature of the subarachnoid hemorrhage. Was it due to a rupture of the vessel walls or to some other factor, such as diapedesis? Was he able to visualize the nature of the hemorrhage?

DR. S. PHILIP GOODHART: What are Dr. Howe's views of the relationship between the local application of drugs to the intracranial tissues and their intravenous administration? Is the local effect identical with that produced by intravenous introduction? Furthermore, is the slowing of the local circulation due to the direct effect or to influence by absorption on the heart action? I wonder how distant circulatory conditions are affected by this local application.

DR. ISIDORE MARGARETTEN: Did Dr. Howe observe the condition of the cerebral vessels and the accumulation of cerebrospinal fluid after introducing alcohol in large quantities into the stomach, instead of giving it intravenously? In my experience, in cases of coma due to acute alcoholic intoxication and in delirium tremens I found no increased tension in the cerebrospinal fluid as estimated by cisternal puncture.

DR. HERBERT S. HOWE: In reply to Dr. Margaretten, we have not introduced alcohol in large quantities into the stomach. When alcohol is diluted with normal saline or dextrose solution, much larger quantities can be injected intravenously without lethal effects than would otherwise be possible.

Concerning the hemorrhages, I have seen them in one or two instances, particularly after the administration of paraldehyde, and while I have not examined them histologically, I think that they are due to a break in the wall of the vessel. One could bring out many interesting things in this connection if there were time, for instance, the injection of inert substances after the injection of alcohol. Alcohol will irritate the endothelium of the blood vessels so that, when india ink is injected, small particles will collect on them much more readily than if a preliminary injection of alcohol has not been given.

As to Dr. Goodhart's question concerning the slowing of the circulation and the death of the animals, I think that the effects are not local but are due to absorption of the drug. In answer to the question concerning local application and intravenous injection of drugs, I believe that the more pronounced effect on local application is due mainly to the greater concentration, as on intravenous injection the drug is diluted by the entire volume of the blood. This work is still gross and primitive, but I think that it has opened a new method for the study of the action of drugs on the cerebral circulation.

VENOUS AND ARTERIOVENOUS ANGIOMAS OF THE BRAIN: A CLINICAL AND ROENTGENOGRAPHIC STUDY OF EIGHT CASES. DR. SAMUEL BROCK and DR. CORNELIUS DYKE.

Following the work of Cushing and Bailey (Tumors Arising from the Blood Vessels of the Brain, C. C. Thomas, Baltimore, 1928), bloodvessel tumors are

divided into two large groups, the true neoplasms — hemangioblastomas — and the vascular malformations. It is with the latter group that this paper deals. The vascular malformations are divided into: (*a*) telangiectases, (*b*) venous angiomas and (*c*) arteriovenous angiomas. These result from defective development of the cerebral or meningeal primordial vascular plexus. In the following we will describe the clinical studies and the roentgenograms made in three venous and five arteriovenous angiomas of the brain.

Case 1 was that of a left-handed man, aged 33, who had suffered from "migraine" for eighteen years and from "tinnitus" and convulsive seizures for three years. A sister was feebleminded. Neural examination gave negative results. The unusual roentgenographic findings of convoluted cerebral calcification pointed to the presence of a venous angioma in the left occipital lobe.

Case 2 was that of a male child, aged 6½ years, with a congenital hyperplastic port-wine nevus of the right side of the forehead, scalp and upper lip (first and second branches of the right fifth nerve) who presumably had a left cerebral hemorrhage at the age of 9 months, following which amentia and right hemiplegia appeared. Roentgenograms disclosed convoluted vascular calcification of the right occipital lobe and left porencephaly.

Cases of this kind are not uncommon. Certain French writers speak of them under the term "neurocutaneous syndrome." Similar roentgenogram findings have been stressed by F. Parkes Weber (A Note on the Association of Extensive Hemangiomatous Naevus of the Skin with Cerebral 'Meningeal' Hemangioma, Especially Cases of Facial Vascular Naevus with Contralateral Hemiplegia, *Proc. Royal Soc. Med.* **22**:431, 1928).

Case 3 was that of a man, aged 21, who gave a definite history of acute epidemic encephalitis in 1925. He showed a large angioma of the right side of the face with a venous angioma of the right retina and blindness of the right eye, ocular palsies, exophthalmos, left mimetic facial weakness, incoordination and mental deterioration. Very likely the right-sided exophthalmos was due to an angiomatous extension into the retro-orbital tissues or cavernous sinus. An enlarged, throbbing right carotid and temporal arteries with a systolic bruit suggested that the venous angioma was undergoing a process of "arterialization."

Case 4 was that of an ambidextrous man, aged 51, who showed exophthalmos, left homonymous hemianopia, pulsating aneurysmal enlargements of the occipital arteries, an extracranial bruit heard over the latter vessels, enlarged heart and carotid arteries and low systolic and diastolic blood pressure, with Corrigan's pulse. Intracerebral calcification was found in the right occipital lobe. The signs of cerebral disease (strengthened by the roentgenogram findings) were believed to be due to an arteriovenous, angiomatous lesion of the right occipital lobe.

Case 5 was that of a left-handed boy, aged 16, with a presumed left temporofrontal arteriovenous angioma, associated with an extracranial (frontal) angioma, an enlarged heart and unusual cardiac murmur, pulsating carotids and tachycardia. An intracranial bruit was heard. The patient had a right homonymous hemianopia. He was mentally retarded. Intracerebral calcification was found in the left frontal lobe. The presence of the loud bruit suffices to stamp the lesion as arteriovenous. Whether more direct vascular communications exist between the extracranial and the intracranial malformations cannot be stated definitely, although the likelihood is great.

Case 6 was that of a woman, aged 25, who developed papilledema, defective vision and a left homonymous hemianopia in the course of one year. Craniotomy disclosed a right frontotemporal arteriovenous angioma. A bruit was heard after operation. Cardiac enlargement, tachycardia, a faint mitral systolic murmur and an extremely low diastolic blood pressure were noted. In this instance the course conformed to that of an expanding intracranial neoplasm — a progression characteristic of the usual arterial angioma as described by Cushing and Bailey.

Case 7 was that of a woman, aged 53, who complained of a gradual diminution of vision, tinnitus and headache for three years. A right lower facial weakness, right homonymous hemianopia, pale optic disks, an intracranial bruit and mental

changes were found. In addition, a low blood pressure and an enlargement of the heart and of the left temporal and the carotid arteries were noted. Sudden death occurred; just preceding it, a spinal tap revealed bloody spinal fluid. The peculiar intracerebral calcification found in the left frontal lobe and the enlargement of the cranial and carotid vessels and of the heart, together with the bruit, pointed to an arteriovenous angioma.

Case 8 was that of an ambidextrous man, aged 34, who gave a history and presented the clinical picture of acute epidemic encephalitis in 1921. In 1930, convulsive seizures began. In 1931, bilateral papilledema with optic atrophy, left homonymous hemianopia, left internal rectus paralysis, nystagmus, right facial weakness, diminution of deep reflexes and peculiar sensory and mental changes were found. A ventriculogram revealed internal hydrocephalus; autopsy showed an unsuspected arteriovenous angioma in the tegmental part of the midbrain (W. E. Dandy).

Comment.—Eight instances of intracranial angioma are described. In four, extracranial vascular lesions coexisted.

The important eye signs were a homonymous hemianopia and unilateral exophthalmos. An unusual instance of venous angioma of the retina is described.

The cardiovascular phenomena in the arteriovenous variety of angioma are of diagnostic significance. They consist of enlargement, of intracranial, cranial, extracranial and carotid arteries and of the heart; a systolic mitral murmur may appear; a mild degree of tachycardia occurs. Low systolic, a much reduced diastolic blood pressure and Corrigan's water-hammer pulse are found. The resemblance of the cardiovascular picture to that in aortic regurgitation is commented on. Reference is made to the studies of Lewis and Drury on arteriovenous aneurysms.

An arterial bruit of extracranial or intracranial origin is an important sign, too often overlooked.

The outstanding roentgenographic findings consist of intracerebral calcification, dilatation and tortuosity of the vascular grooves in the bones of the skull. The convoluted calcification found in the venous angiomas is pathognomonic.

Methods of treatment are briefly discussed.

This article will appear in full in a forthcoming issue of the *Bulletin of the Neurological Institute of New York.*

DISCUSSION

DR. FOSTER KENNEDY: The diagnosis in these cases is sometimes easy. The roentgenograms will give authentic information. The frequent occurrence of so much left-handedness in these cases suggested something to me. Daresti believed that right-handedness is due to the fact that the human embryo is placed in the uterine cavity more on the left than on the right side, so that the right arm and leg swing more freely than the left. It struck me that, in embryos swung in a manner contrary to the prevailing tradewind, as it were, the circulation as well as the handedness would be disturbed, and the observation of a conformity between left-handedness and the presence of these abnormal congenital conditions was not fortuitous.

I have a number of observations of a clinical nature on the presence of nevi and vascular malformations in the diploe, dura and brain. Lately I was asked for an opinion concerning a man taking action against the State of New York because he had received an injury in a motor car from a defective roadway. The injury was slight; he was thrown against the top of the car, had a bad headache and was confused. The headache persisted and got worse. It was so bad that he had to stay at home. On the eighth day after the injury he became stuporous; he lost and regained consciousness continuously and had right hemiplegia and papilledema. He remained in that condition for a number of weeks and was seen by many physicians in two hospitals. He recovered from the acute symptoms, but retained a right hemiplegia. The case was taken up by a beneficent lawyer, who managed it for a period of years. The case was thought to be one of

Spätapoplexie; it was nothing of the kind. The patient had, what nobody had noticed, a triangular nevus exactly over the left motor area. That nevus, of course, has its homolog in the dura. He received an injury to it and suffered a dural hematoma, which took seven or eight days to form, with the production of the hemiplegia. Nevi on the face and scalp have their corresponding lesions throughout the area below which they occur; if they are injured, they at times spontaneously break.

A Case of Congenital General Analgesia. Dr. George Van Ness Dearborn.

The case is that of a man, aged 54, who was born in Prague. He attended high school for two and one-half years, and was a musician for four years in the United States Marine Corps. He seemed normal in all respects, aside from the fact that he could recall no experience of pain except headache. Ten injuries occurred to various parts of his body, including a burn of a finger, an "acute condition of the middle ear," a fracture of a bone, one-quarter of a crucifixion and several incised wounds since he was 7 years old, without giving him so-called "physical" pain. He also had an ulcerated tooth. For nineteen months he earned his living on the vaudeville stage as "The Human Pincushion." Thrice daily, two or three score of sterilized ordinary pins were pushed into his body "anywhere save in the belly or the groin."

Once he staged his own crucifixion; a gold-plated spike had been driven through one hand into the cross, when a woman in the audience fainted, and the remainder of the "stunt" was omitted.

As to the explanation of this phenomenon, there is no sign whatever that hysteria or any other psychiatric condition, masochism for example, is the etiologic factor in this generalized analgesia. The patient himself explains his lack of pain as due to his mental concentration "away" from the trauma or the stimulus. The physical side of attention-concentration, however, is wholly lacking.

On must postulate some congenital defect in the central pain tracts or centers. Until more is certain about the site of the defect, however, no commitments seem to be warranted.

DISCUSSION

Dr. Paul F. Schilder: I think that perhaps the term "analgesia" applied in this case is not exactly appropriate. The patient can distinguish between the point and the head of a needle. It is not so much that pain is lacking, but that the emotional reaction to it is absent. These cases are of great interest. I have observed one almost similar case. In my case it was noteworthy that the reaction of the pupils to pain, as well as the reaction of the pulse and of the blood pressure, were absent. I studied this patient carefully. The lack of pain reactions was familial; the patient's mother had the same insensitivity. Another point of interest is that he was an extremely sadomasochistic person. Sadomasochism impaired his normal sex function; when these cases are thoroughly studied one finds an extreme sadomasochism in all of them. There are two possible explanations: one, that there is a defect in the pain apperceptive system, an agnosia for pain. The possibility exists. I have studied a series of cases of patients with brain lesions who have had agnosia for pain. A lesion of the supramarginal gyrus is responsible for the inadequate apperception of pain. It is possible that this part of the brain is underdeveloped in this case. Moreover, perhaps these patients for some reason repress their pain. They are certainly not hysterical in the ordinary sense. It may be one of the deep-lying perversions. In this respect it is remarkable that in one of the older works of Lombroso one finds remarks to the effect that criminals often show insensitivity to pain. In Bellevue Hospital I observed two cases in which the sensitiveness to pain was much impaired. One of the cases was rather famous: it was that of Baker, who had killed a watchman by stuffing cyanide down his throat. He showed extreme hatred and marked sadistic tendencies, which went back to early experiences in childhood. The man

said that he had probably killed ten or eleven more persons; whether that is true or not, I do not know. Similar disturbances can be observed in extremely sadomasochistic persons. These cases are important, because the problem of pain is of great significance in all fields of medicine. After all, in the symptomatology of internal disease, pain plays a great part. Our whole attitude and feeling determine the final nature of the symptom. In cases I observed there was little reaction to pain coming from ulcers of the stomach, so that these problems are of interest in general medicine.

CHICAGO NEUROLOGICAL SOCIETY

Regular Meeting, Feb. 18, 1932

A. B. YUDELSON, M.D., *President, in the Chair*

TUMOR OF THE PINEAL BODY INVADING THE SYLVIAN AQUEDUCT. DR. VICTOR E. GONDA.

A. B., a white man, aged 45, entered the Cook County Hospital twelve days before death. He had been suffering from a mild frontal headache that had become progressively worse. Nine days before admission (exactly three weeks before death), the headache became very severe and was associated with vomiting on three occasions. The patient had to leave work and was sent to a hospital by his physician. Two spinal punctures were performed. Vomiting stopped after these punctures, but the headaches were just as severe. The patient returned home, and again vomiting occurred two or three times daily.

On entrance to the Cook County Hospital, on March 23, 1931, the patient was semistuporous but able to walk; the gait was ataxic and wabbling. There was a slight drooping of the left upper eyelid; he was unable to look to the extreme right, and he also complained of double vision. The pupils were unequal, the left being larger than the right; both reacted sluggishly to light and in accommodation. The fields of vision roughly appeared to be normal. There was a suggestion of a choked disk. The tongue showed some tremor but no deviation. There was no deafness, and no other involvement of the cranial nerves was demonstrated. There was slight past-pointing with the right forefinger to the right. The biceps, triceps and radial periosteal reflexes were somewhat sluggish bilaterally. At the beginning the right patellar reflex was sluggish and gradually disappeared completely, while the left knee jerk was rather lively. Both achilles jerks were sluggish. The plantar responses were normal; the abdominal and cremasteric reflexes were very lively. The neck became rigid. A slight Brudzinski sign of the neck and a marked Kernig sign were present.

Roentgen examination of the skull, the Wassermann tests of the blood and spinal fluid and urinalysis gave negative results. The white blood count was 14,600; a differential count revealed 81 per cent polymorphonuclears, 15 per cent lymphocytes and 4 per cent monocytes.

Repeated spinal punctures disclosed the fluid to be under markedly increased pressure; the fluid was bright red, and when the supernatant fluid settled, it was xanthochromic. A direct smear did not reveal any organisms, but the first culture yielded pneumococci. At that time the diagnosis of tumor of the brain was changed to meningo-encephalitis. However, subsequent cultures of the spinal fluid were sterile.

The patient remained semistuporous and toward the end became delirious. The pulse rate varied between 54 and 68. The patient was afebrile on entrance to the hospital, but the temperature rose to 101 F. during the rest of his stay, a terminal elevation to 106.4 F. occurring with clinical signs of bronchopneumonia.

Dr. Jaffé reported the following postmortem observations:

The right pupil was narrower than the left. After the skull cap had been removed, the dura mater was found to be stretched tightly over the cerebral hemispheres. The convolutions were flattened, and over the posterior half of both hemispheres and the superior aspect of the cerebellum there were recent dark purple-red extravasations of blood.

In the region of the pineal body and substituting it, there was a sharply circumscribed, moderately firm, light pinkish-gray mass, which measured 15 by 10 by 16 mm. It was attached to the tela choroidea, the two internal cerebral veins crossing its upper aspect. The mass continued into the lamina quadrigemina and in one place had broken into the sylvian aqueduct, which was almost completely filled by it. The lateral ventricles were only moderately distended and were filled by a blood-tinted fluid.

The following microscopic observations were reported by Dr. Percival Bailey: The tumor was composed of cells with very little cytoplasm and oval, rather vesicular nuclei. Each nucleus had one, sometimes two, nucleoli and fine scattered grains of chromatin. The nuclear membranes were often wrinkled. No mitoses were seen. The cytoplasm was stringy and very scanty. The cells were scattered fairly evenly. Some were collected around small, thin-walled, vascular sinuses, but this perivascular arrangement was due to degeneration of the cells farther from the vessels. Connective tissue was confined practically exclusively to the walls of the blood vessels. There were a few nodules of calcium in the walls of the vessels.

I am reporting this case for the following reasons: 1. Primary tumors of the pineal body are rare. Among 3,000 cases of verified intracranial tumors in the collection of Cushing, this type occurred in about 0.5 per cent. 2. The tumor in the case reported had caused no symptoms up to three weeks before death. 3. It produced almost all of the neurologic signs and symptoms characteristic of tumors of the pineal body in the adult, which are practically the same as those of the adjacent quadrigeminal body. 4. I wish to emphasize the evolution of the symptoms and findings when bleeding occurs in this type of case and to warn against hasty changes in diagnosis when such a complication arises.

Bleeding into the ventricles, followed by the appearance of blood in the subarachnoid space, superimposes the symptoms of meningeal irritation on the original picture due to the tumor alone. That such bleeding may occur is evidenced by its occurrence in two cases reported by Dr. Horrax and Dr. Bailey (Tumors of the Pineal Body, ARCHIVES OF NEUROLOGY AND PSYCHIATRY **13**:423 [April] 1925). In their cases, as in the one reported, the appearance of the Kernig sign and differences in the deep reflexes were findings that differentiated the cases in which bleeding occurred from those in which it did not occur. (It might be of interest to note that two of the tumors in which hemorrhage occurred were of the embryonic type, and the third was probably also of this type.)

DISCUSSION

DR. PERCIVAL BAILEY: The pineoblastomas contain little connective tissue and are soft. This may account for the ease with which hemorrhages occur in them. The pineolomas of the adult type are much firmer.

CALCIFIED ANGIOMA OF THE BRAIN: REPORT OF A CASE. DR. JOHN L. GARVEY.

Angiomas of the brain associated with nevi of the trigeminal area are relatively uncommon. Calcification of cerebral angiomas associated with facial nevi has been observed even less frequently. The roentgenographic manifestations of the calcification are characteristic. In all of the cases reported the calcified area has been observed above the tentorium cerebelli and on the same side as the facial nevus. The calcification seems to follow the surface of the brain and to extend into the cerebral tissue like an inverted cone.

A girl, aged 15, was examined because of attacks. She was born when the mother was 42 years of age. The patient had always been regarded as being

somewhat below par mentally. The family used the term "inferiority complex" to describe partially her mental state. When the patient was 4 or 5 years of age she underwent an operation on the left eye for the correction of strabismus. When she was about 15 months of age she began to walk. The attacks described by the mother indicated that the patient had mild convulsive attacks with momentary loss of consciousness and turning of the head and trunk to the left. During the year previous to the writing of this report, these attacks were more severe than at any other time. The attacks had occurred since early childhood.

Neurologic examination gave essentially negative results, except for some ocular palsies, probably of congenital origin, and a defect in the visual fields, the left field showing a defect in the inferior temporal quadrant and the right field showing a narrowing of the entire nasal field. Over the right side of the forehead there was a slightly raised port-wine type of nevus. The same type of lesion was also present over the upper lid of the right eye and within the hairline. The nevus was entirely within the area of the right trigeminal region. Roentgenographic studies of the skull revealed a calcified area in the right occipital pole similar to the calcifications seen in previously reported cases of angiomas of the brain associated with trigeminal nevi.

DISCUSSION

DR. PERCIVAL BAILEY: The association of the angiomas of the surface of the brain and angioma of the face is not difficult to understand when one remembers the method of development of the blood vessels in the region of the head. In the embryo there is one sheet of anastomotic vessels between the brain and the surface of the skin, and this plexiform mass is broken up into several sheets, one in the meninges, one in the subcutaneous tissues and one in the pia mater. This occurs early in embryonic life, and one can easily understand that when the mass is split up by the formation of the skull and the dura mater, anything that influences this plexiform arrangement will cause an anomaly that affects simultaneously the brain, the face and the meninges; that condition is found in this case. I have not been able to explain satisfactorily why such angiomas are almost invariably found in the occipital region.

POSTURAL PERSISTENCE IN POSTENCEPHALITIS. DR. LOWELL S. SELLING.

Postural persistence has been studied by means of the test of Schilder and Hoff. The technic followed was: 1. The subject, blindfolded, was placed erect, with arms outstretched, palms down, and a measuring instrument was placed between the tips of his index fingers. 2. The control (usually the right) hand was held by the observer in front of the zero of the gage, and the hand to be tested was lowered by the observer to an angle of from 45 to 60 degrees. 3. The hands were held in these positions for twenty seconds, when both were released. The subject was then told to raise the left hand to the level of the right, and a reading of the result was made.

In fifty normal persons the deviation below the level of the control hand, ranged from 3 to 7 cm. In thirty-two patients with postencephalitic parkinsonism, the range of deviation was from 0 to 3 cm.; in twenty-four cases the reading was 0. In seven cases there was an apparently negative deviation; that is, the left hand was raised above the control hand, which was found to be due to the dropping of the control hand. In ten cases in which there were only slight or doubtful signs of parkinsonism following epidemic encephalitis, the range of deviation was from 0 to 6 cm., approximately normal; however, in four of the ten there was either a reading of zero or a pseudonegative result. In a group of fourteen persons who had definitely had epidemic encephalitis but who showed no neurologic signs, though disorders of behavior were present, the results were discrepant; in three the result was "negative," and in three the deviation was greater than average. In two postencephalitic cases with unilateral signs of extrapyramidal damage, the

postural persistence phenomenon was diminished to 1 cm. on the affected side and approximated normal on the other.

As a result of these observations, I conclude that loss or diminution of postural persistence is corroborative of parkinsonism; that it often indicates the presence of actual extrapyramidal damage, and that it may corroborate the existence of such damage in cases of behavior disorder.

DISCUSSION

DR. PAUL L. SCHROEDER: In the behavior clinic, especially with children in whom the diagnosis of encephalitis seems justified by the behavior, the history is often confused and sometimes unobtainable, even when the neurologic findings are definite. We are always glad of methods that tend to confirm the diagnosis, but feel that it is desirable to have it based on neurologic findings.

DR. ROY R. GRINKER: I have been using the Lagebeherrung test in the neurologic clinic to determine whether it was of any help in the localization of tumors. I must confess that I have not used such accurate means of determining the exact position, but I have usually found that the position of the two extremities was equal. There was usually no deviation. From the cases in which I have used this method in a rough way, I have come to the conclusion that deviation was more abnormal than no deviation in most patients with neurologic conditions. I wonder whether one could obtain more accurate data as to what is and what is not parkinsonism by using the method in other cases. According to the data presented, I do not think that one could rely on the results of this test for a diagnosis of a behavior disorder as due to chronic encephalitis. I am not sure that one is justified in making the statement that the significance of the parkinsonian rigidity is that of a pallidal lesion. I do not think that the findings in encephalitis reported in the literature would justify that conclusion, and I do not think that the postural persistence would justify the statement that the presence of the behavior disorder is due to a lesion of the basal ganglion.

I suppose that the word postencephalitis was used to mean chronic encephalitis.

DR. LOWELL S. SELLING: I think that Dr. Grinker's criticisms are well made. Perhaps I should have said "chronic encephalitis," but in the clinics for behavior disorders "postencephalitis" is still acceptable.

As to the use of the tests in neurologic clinics and the suggestions as to the localization of the function, I mean these statements to be only suggestions, although there are findings to justify the conclusions. On the other hand, the tests have been made in a number of neurologic cases over a considerable period of time, and it has been found that in many instances lowering of the arm could be elicited, while in cases of parkinsonism this sign was absent. I do not think that Dr. Grinker meant to say that postural persistence is absent in normal cases, for it is not.

A UNIQUE TYPE OF SPEECH DISTURBANCE IN EPIDEMIC ENCEPHALITIS. DR. D. M. OLKON.

A man, aged 36, complained of a difficulty in speech that had existed for three years. He had been well until six years before he came to me, when he had had "flu" with fever, sore throat, headache, malaise and double vision for about ten days. After this brief illness he resumed work without unusual difficulty. About three years before this paper was written he experienced a slowness of speech which became progressively worse; two years later the movements of his fingers and arms as well as mastication became slow, and speech became deranged.

On examination the facial expression was masklike; the hands were held in a fixed attitude; there were cogwheel rigidity of the muscles of the neck and arms and a coarse tremor of the tongue and hands. The Aschner sign was present, and sialorrhea was marked. The gait was slow. All of the reflexes were normal, and there was no paresis or paralysis of the muscles of speech. Sensation was intact.

The speech was whisper-like and slow, without scanning. The muscles of speech were in a state of fixity; the lips, the facial muscles, the tongue and the pharynx barely moved when the patient spoke, and the words came as though the larynx pushed them through the nose and between the teeth, with a complete loss of tonal pitch. The term dysphonia was selected because of the deranged vocalization without neural involvement. I called this disturbance in speech a dysphragic and asynergic dysphonia because of the profound disturbance in muscle tonus.

This disturbance points to a sequel of encephalitis, without the focal manifestations of glossopharyngeal or vagal involvement, but rather with a high grade of disturbance of muscle tonus and vasomotor control in which the muscles of speech were more selectively involved.

DISCUSSION

DR. VICTOR E. GONDA: After listening to the description of the signs and symptoms which in this case all pointed to an involvement of the extrapyramidal motor system, I think that one must come to the conclusion that this disturbance in speech is only a part of the so-called striatal pseudobulbar palsy, described by Vogt, from which the patient is undoubtedly suffering. Why should one give another name to a part of this disease entity and complicate still further this symptom complex?

DR. ROY GRINKER: I think that the term pseudobulbar palsy is worse than "dysphragia"; neither means anything as a label. I think that the research of Kinnier Wilson can be applied to the phenomenon that Dr. Olkon has described. Wilson found that there was a definite weakness in the small muscles of the hands, particularly the distal ones, and with his tracings was able to show that there was not only an initial weakness, but that with increasing fatigue more weakness was evident. I do not think that Dr. Olkon has demonstrated that there was any change in the tone of the muscles. There may be weakness in the small muscles without any change in tone, but Dr. Olkon showed some remarkable tracings of fatigue such as occur in myasthenia gravis. I wonder whether he is not dealing with changes in muscle strength rather than muscle tone.

DR. D. M. OLKON: I agree with Dr. Gonda that the condition described belongs to the extrapyramidal pattern of muscular disturbances, which was stated in the paper. I am also in sympathy with his objection to the term dysphragia. I objected to it at first, but not finding another single term more expressive of this pattern of speech disturbance I thought that this term came closest to describing it; I admit that it is not in keeping with the usual terminology.

In answer to Dr. Grinker, I may take refuge in the statement that a definition of "tonus" has not been agreed on thus far. The various views on tonus are conspicuous for their disagreement. I may ask what is meant by weakness of muscles. One may answer that in such disturbances the activity of the muscles is at fault. But, again, what is the nature of this faultiness? My notion is that primarily there is an interference with cellular activity in its nutritive and oxidative balance, which must interfere with the balance in energy production and lead to faulty integrative equilibrium. In a case like the one under discussion, I do not know what term one may use other than tonus disturbance. I clearly showed that the deficiency of the muscles of speech in this case did not apparently connect with concomitant disturbances of the peripheral, cerebrospinal and sympathetic innervation *per se*, so that there was no alternative but to think of the condition in terms of a tonus imbalance. Whether the striatum actually controls the physiologic tonus component or whether it is an auxiliary to other neural factors, I do not pretend to settle. In this particular case of encephalitis the predominant signs, clinically, were not of the neural type, but were rather a disturbance of the energy of the muscle itself, which affected the muscles of speech in a more perceptible way. Hence, the atonicity of the muscles, and not the neural apparatus, was the striking feature clinically.

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

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W. J. MIXTER, M.D., *in the Chair*

A NEW THEORY OF THE ORIGIN OF DUPUYTREN'S CONTRACTURE. DR. HALE POWERS.

The prevailing opinion has been that Dupuytren's contracture is the result of continued local trauma or of a low grade inflammatory process. I knew of no other explanation until I studied a case in which the contracture, some areas of scleroderma and a nonpigmented, hyperhydrotic area were all observed in the sensory area of the ulnar nerve. On reviewing the literature, I was impressed with the fact that the contracture almost always begins in the area of the ulnar nerve. Walter Scholle, in the *Deutsche Zeitschrift für Chirurgie* (**23**:328, 1930) quoted the statistics of Noble and Smith and of the *Polyklinik* of Leipzig. By combining these two statistical tables, I found that the ring or little finger, or the ring and little finger were the only ones affected in 94 of 113 cases. The first fingers affected have been the ring and little fingers in all cases that I have seen, with the exception of hereditary cases. In the literature the frequent association of Dupuytren's contracture with trophic disorders, and with neurologic and pulmonary conditions is impressive. In my own series of 13 cases there is positive evidence of past or present pulmonary conditions in 9, while roentgen findings are suggestive in one or two others. In 1922, Janssen made a pathologic study proving that the process is a purely hypertrophic one, in which mechanical irritation and inflammation play no part. Several German writers alone have suggested that it is a neurologic condition primarily. Kurt Iklé suggested that irritation of the trophic centers in the spinal cord may be primary, but if this is true the distribution should be segmental. Nippert believed that the primary cause is hyperirritability of the whole vegetative nervous system, but to me that seems to be true only in the hereditary cases. Dupuytren observed the condition in the plantar fascia. I have seen a case which I believe to be one of early plantar Dupuytren's contracture associated with a severe chronic left postero-inferior pleurisy, with frequent pain and friction rub.

Any satisfactory theory of Dupuytren's contracture must explain its usual beginning in the ulnar distribution and its frequent association with pulmonary conditions. The sympathetic ganglia below the middle cervical are in close relation with the pleurae. In the presence of pulmonary disease I believe that they may be irritated and hyperactivated by elevation of temperature, by mechanical irritation in coughing, by an increased supply of blood or in other ways. This irritation of the sympathetic ganglia, I believe, results in hypertrophic changes at the periphery. This accounts for the clubbing of the fingers in tuberculosis and for the pulmonary osteo-arthropathy of Claude Bernard. In the familiar syndrome of hypertrophied thyroid with exophthalmos, both glandular hypertrophy and exophthalmos are symptomatic of ganglionic hyperactivity, possibly due to an emotional state. I believe that the usual beginning of Dupuytren's contracture in the ulnar area must be accounted for by the fact that the ulnar nerve arises from the roots of the eighth cervical and first dorsal, therefore being nearer to the stellate and thoracic ganglia than are the other nerves of the brachial plexus, and I assume that it carries trophic fibers to the periphery, admitting, in this detail, a conflict with present anatomic concepts. My main thesis is that intrathoracic disease produces irritation of the ganglia and that there is then hyperactivity of the ganglia, which results in Dupuytren's contracture and other trophic changes at the periphery.

DISCUSSION

DR. W. J. MIXTER: Dr. Powers has delved into a large subject. Dupuytren's contracture would come in the same category and might follow the same distribu-

tion as Raynaud's disease. What comes to mind immediately is that if Dupuytren's contracture is the result of sympathetic overstimulation, then can one relieve it by operation on the sympathetic? A cure by surgical intervention is so satisfactory.

DR. B. T. BURLEY: A young man was in my office today with a beginning Dupuytren's contracture. He had been in the army, was atonic and gave a history of having had peptic ulcers. The condition of the hand had been noted for only a few weeks. The involvement was of the middle and ring fingers. I should be interested to know what treatment would be advisable in this case. It is too early for operation.

DR. D. MCK. RIOCH: The problem of the so-called "trophic fibers" is still open, and it is not justifiable at present to use this hypothesis except most tentatively. The ulnar distribution of Dupuytren's contracture cannot be referred to the stellate ganglion, as almost the whole of the postganglionic supply to the arm passes through the upper three thoracic ganglia. The preganglionic fibers, according to O. Foerster, of Breslau, leave the cord with the fifth to the ninth thoracic nerves, which is of no localizing value in the present case, but may help to explain the failure of surgical treatment of Raynaud's disease, in which operation has been confined to the upper three ganglia.

DR. H. POWERS: I do not know a great deal about the anatomy that has been discussed. I wish some one would explain this ulnar distribution. It must be explained in some manner. I wish that anatomists would give some explanation. Dr. Mixter, do you relieve the pain by surgical intervention?

DR. W. J. MIXTER: I think that removal of local contracture removes pain.

DR. H. POWERS: Some patients have pain that is referred to the shoulder.

THE RELATIONSHIP BETWEEN WATER BALANCE, SPINAL FLUID PRESSURE AND EPILEPTIC CONVULSIONS. DR. FRANK FREMONT-SMITH, DR. HOUSTON MERRITT and DR. W. G. LENNOX.

Numerous investigators have emphasized recently the relationship of water metabolism to convulsions. Rowntree, Kubie and others have produced convulsions in animals by giving large quantities of water by mouth or by stomach tube. McQuarrie has given epileptic children pitressin and water, causing a retention of water and the precipitation of convulsive attacks. Gamble studied the water balance in an epileptic patient and found that there was an alternate release and retention of body fluid, release occurring during the days on which seizures occurred. Other studies also indicate that in some patients the attacks are related to a disturbance in water balance. The dehydration treatment instituted by Fay and by McQuarrie was for the purpose of preventing this disturbance. The beneficial effects of the ketogenic diet have also been ascribed to the diuresis and the resulting state of dehydration which accompany the establishment of ketosis.

At operations and at necropsy there is often found in epileptic patients an increase in the subarachnoid fluid, overlying an atrophy of the cortex. This can also be demonstrated in some cases by encephalography. It has generally been assumed that such collections of fluid in epileptic persons have origin in the same manner as in cases of dementia paralytica, cerebral arteriosclerosis, etc.; that is, they are secondary to the atrophy of the underlying cortex — hydrops ex vacuo. Fay and Winkelman, however, claimed that in epileptic persons this fluid has collected in the subarachnoid space as the result of an impairment of the function of the pacchionian granulations, and attribute the "shrinkage of the adjacent convolutions to the effects of hydraulic pressure on the walls of these fluid channels producing an ischaemic type of pressure atrophy." Fay stated further that the convulsive attacks are due to hydraulic pressure, specifically applied, of the proper degree and confined within the cortical subarachnoid space.

These statements do not conform to the generally accepted ideas as to the pressure relationships in the central nervous system, and since there have not been any careful studies of the relationship of intracranial pressure to fluid intake or

balance, my colleagues and I undertook to make such a study at the Boston City Hospital. A group of epileptic patients agreed to undergo the necessary tests, and we endeavored to make observations in order to determine the following: 1. Do epileptic persons excrete water normally? 2. What is the effect on the intracranial pressure of the following procedures? (*a*) the rapid ingestion of a large amount of water; (*b*) the rapid ingestion of a large amount of water after the patient has been rendered unable to excrete the water by means of the antidiuretic principle of the pituitary gland (pitressin); (*c*) the ingestion of large amounts of water (from 4 to 6 liters per day) continued for a period of five days; (*d*) very restricted water intake for a period of five days.

Method Used.—The patients chosen for the study were all male and were chiefly adult. They were all subject to convulsive attacks at rather infrequent intervals. They were placed in a quiet room under basal conditions. Lumbar puncture was made under procaine anesthesia. The intracranial pressure was observed continuously, and the variations were recorded at intervals of one minute. In every test the pressure was recorded for at least thirty minutes in order to obtain an accurate base line, or initial pressure.

In the experiments in which the patients were required to drink a large amount of water in a short interval, lumbar puncture was performed, readings of the intracranial pressure were made for a period of thirty minutes and then the patients were allowed to drink from 1 to 2.5 liters of water within a period of from forty to sixty minutes. Readings of the intracranial pressure were recorded during this period and for one to two and one-half hours after the completion of the drinking. The Fremont-Smith modification of the Ayer spinal puncture needle and manometer were used throughout the tests, and the pressure readings, expressed in millimeters of spinal fluid, are corrected for the capillary pressure of the manometer. A spirit level was used to determine whether the lumbar needle was at the same level as the occipital protuberance. At the end of each test, fluid was removed for a cell count and chemical study.

Findings.—In ten patients in whom the effect on the intracranial pressure of the rapid ingestion of from 1 to 2.5 liters was studied, it was found that the average pressure for the thirty minute period before drinking the water was 137 mm., the average pressure for the forty to sixty minutes required to drink the water, 139 mm., and for the first and second thirty minutes after completion of the water drinking 145 and 138 mm., respectively. It was also found that these patients excreted during the test period approximately 90 per cent of the water ingested.

In seven cases in which the patients were allowed to drink a large amount of water in a short interval, but who were prevented from excreting this water by the injection of pitressin, it was found that the pressure increased from the initial average of 141 to 150 mm. during the period of water drinking, and to 193 and 203 mm. for the first and second half-hour periods after the completion of the water drinking. Two of the patients had convulsions within an hour after the completion of the test. This was considered significant, as these patients had a very low intracranial pressure and presumably an undistended subarachnoid space as a result of the fluid removed.

To exclude the pitressin as the cause of the increase in intracranial pressure, four tests were made in which pitressin alone was given to the patient. In these the pressure was 131 mm. in the control period and 139 and 138 mm. for the first and second thirty minute intervals afterward.

In three cases in which the intracranial pressure was determined after five days each of a low and a high intake of water, it was found that the average intracranial pressure was 151 mm. after the period in which the patients were on the regular ward diet and "normal" fluid intake, 153 mm. after the patients had been taking from 4 to 6 liters per day for five days, 165 mm. after the patients had been on a diet with very low fluid intake (from 0 to 200 cc. per day) for five days. Although these figures indicate that there was little change in the

intracranial pressure with change in the intake of water in these persons, only one of the patients had a convulsion during the period of a low intake of fluid, while all three of the patients had convulsions during the period of high intake of water.

Conclusions.—1. Variations in the level of fluid intake both in acute and prolonged experiments had no appreciable effect on intracranial pressure, provided the diuresis was normal. 2. When diuresis is inhibited by pitressin, the drinking of water is followed by a rise in intracranial pressure. 3. Whatever influence variations in the level of fluid intake have on the frequency of convulsions, this influence does not result from variations in intracranial pressure or dilatation of the subarachnoid space.

DR. J. B. AYER: I think that Dr. Fremont-Smith might have added that in epilepsy, when no tumor or gross pathologic change exists, the fluid pressure is not elevated; at least this is the finding in our cases. If Fay's conception is correct, the cerebrospinal fluid pressure should be increased, and presumably would be transmitted as an elevated pressure to the lumbar sac. In the brains of animals injected intravenously with distilled water, there was found not only increased spinal fluid pressure, but on histologic examination perivascular and pericellular spaces were found to be dilated. Have you been able to check your cases pathologically?

DR. I. HENDRICK: What is the effect of pitressin and water drinking in nonepileptic patients? Is it different from that in the present group?

DR. K. BOWMAN: Would this study yield any information of value in regard to headaches due to lumbar puncture? Would the administration of water and pitressin together have any effect in relieving headache after lumbar puncture?

DR. J. B. MCKENNA: I believe that Fay and Winkelman also stated that in cases of bloody spinal fluid following cerebral trauma there is a reaction in the pacchionian bodies to the red blood cells, as shown by Weed, and that the absorption of the fluid is hindered. Dandy and others have shown by encephalography that the cortical atrophy following trauma is largely confined to the frontal and parietal lobes. Dr. Fremont-Smith, do you apply this pressure theory to these cases and, if so, how do you account for the cortical atrophy following cerebral trauma?

DR. H. MERRITT: In reply to Dr. Ayer, it is my belief that Fay regards our pressure readings on epileptic patients with some suspicion. He uses the mercury manometer and claims that the results obtained are more accurate. We have made double punctures and made simultaneous readings with mercury and water manometers. The readings were remarkably similar, and we believe that the water manometer is much easier to read and is just as reliable as the mercury manometer.

In reply to Dr. Hendrick, we have not made any tests on nonepileptic patients, but there is nothing to make us believe that the giving of pitressin and water has a different effect on the intracranial pressure in epileptic persons from what it would have in normal persons, as pitressin acts as an antidiuretic in both groups.

DR. F. FREMONT-SMITH: Headaches due to lumbar puncture are in all probability hypotension headaches, resulting from leakage of fluid through the hole in the dura produced by the needle. If this is true, it is difficult to see how raising the intracranial pressure by the injection of pitressin and the drinking of water could stop the headache. It would seem more likely that this would only open the hole in the dura more widely. In reply to Dr. McKenna, we have not only many cases of cerebral trauma with bloody fluid but also cases of acute subarachnoid hemorrhage. Those cases do not show atrophy or a prolonged high intracranial pressure. Three or four lumbar punctures cause the pressure to decrease within a few days and to remain normal. The explanation of atrophy following trauma is that it is the result of petechial hemorrhages in the brain. I think that Dr. Merritt deserves credit for the care he has taken in the measurement of the pressure in these cases. I believe that there are good data.

DR. W. J. MIXTER: In the question of headache due to lumbar puncture, I found at operation in one patient the hole made by the needle at lumbar puncture six days previously.

INVOLUTION MELANCHOLIA. DR. NEILS L. ANTHONISEN.

Dr. Anthonisen presented three patients with depression in the involutional age. In these he endeavored to demonstrate that a study of the present reactions, together with the past histories, gave understanding as to why the injuries received (loss of money) became the precipitating factors of psychoses, and also gave indications as to the prognosis before the development of obviously unfavorable signs (untidiness, distorted ideas and apathy). The formulation of personality make-up implied a formulation of constitutional and hereditary factors.

DISCUSSION

DR. F. H. PACKARD: The prognosis of involution melancholia has been a subject of much interest to me for many years. In the review and analysis of many such cases, procedure along lines similar to those suggested by Dr. Anthonisen has been attempted, from time to time. Theoretically, other things being equal, an analysis of personality traits and the general make-up of the patient with relation to the particular circumstances and conditions in which he finds himself should be important prognostically. In my experience, however, I have found that prognoses based on such an analysis are not always accurate. The prognosis was often more favorable in patients who in earlier life had had a previous attack than in those whose first attack came at the involution period. In the first instance, the history of a previous attack or attacks indicates the probability that the patient was of an unstable make-up fundamentally, and the attack at the involution period was merely the manifestation of another abnormal wave and not necessarily associated with, or due to, physical involution. In the second instance, in which the first attack comes at the involution period, it seems possible that the mental upset is associated with a physical involution process.

My experience has convinced me that it is unsafe to make an unfavorable prognosis in cases of involution melancholia, even in ones of long standing, until symptoms of irreparable loss can be demonstrated. The most important of these are: First, a loss of display of emotional reaction proportionate to the content of the ideas and delusions. Second, and accompanying this loss of emotional reaction, is a narrowing of the mental horizon; the patient no longer talks about, thinks about or is interested in any subject or person beyond his reach and vision. In many cases of long duration in which, theoretically, recovery might be expected, I have found that the patients have been overtaken by cerebral arteriosclerosis with consequent organic symptoms precipitating the final picture. I am strongly inclined to believe that there is an underlying pathologic condition which is an etiologic factor in all cases in which the patient fails to recover.

DR. N. ANTHONISEN: I never dare to say that it is not possible for a patient to get well. Analysis is frequently not satisfactory. What I wish to present here is the idea that careful study of the case early in its course may yield valuable information for the formulation of the prognosis.

THERAPEUTIC PROCEDURES IN PSYCHIATRY. DR. DONALD GREGG, Wellesly, Mass.

In the classification of the psychoses by Kraepelin, as modified and used by the New York State hospitals, sixteen of twenty classes, or 80 per cent, are readily considered organic in type. The remaining four classes, namely, manic-depressive psychosis, dementia praecox, paranoia and psychosis with psychopathic personality by some may be considered functional in origin. Thirty years ago, William James stated: "A certain amount of brain physiology must be presupposed or included in psychology." From the point of view, then, of bodily

experiences and more particularly brain experiences, what today can be done in the way of therapeutic procedures?

The organic psychoses are: traumatic psychoses, senile psychoses, psychoses with cerebral arteriosclerosis, dementia paralytica, psychoses with cerebral syphilis, psychoses with Huntington's chorea, psychoses with tumor of the brain, psychoses with other brain or nervous diseases, alcoholic psychoses, psychoses due to drugs and other exogenous toxins, psychoses with pellagra, psychoses with other somatic diseases, involution melancholia, psychoses with mental deficiency, epileptic psychoses and undiagnosed psychoses. For this organic group, it is evident that treatment lies in the treatment of the underlying condition.

In the remaining groups one should expect to find a pathologic process in the prefrontal areas, which are logically considered by Tilney and others as the seat of reason, judgment and discrimination — the bases of human experience and personality. Paleokinetic activity is instinctive, according to reflex and routine. Neokinetic activity, on the other hand, introduces the time element, with inhibitions and delays giving opportunity for reflection and selection. A shift from neokinetic to paleokinetic activity is commonly seen in fatigue, illness, old age and deterioration.

The acutely manic phase of manic-depressive psychosis is best handled in large hospitals, where prolonged baths and a minimum of restraint in quarters well equipped for such patients are available. The best of nursing care with careful check as to focal infection and systemic disease is essential. A minimum of sedative drugs shortens the period of convalescence. Every depressed patient is a facultative suicide, especially at the beginning and during convalescence. The use of oxygen-tent inhalations seemingly is of some benefit as a physiologic stimulus, having a soothing effect and adding to the comfort of the patient. Oxygenation without expenditure of energy and without the complications of contacts has distinct advantages. Whatever raises the question of inadequacy is to be avoided.

In dementia praecox the treatment is largely symptomatic. Routine occupational therapy is invaluable. As this is the great dump heap of psychiatry, whatever can be done to rescue persons from it by attention to focal infections, glandular abnormalities, intercurrent diseases, etc., is, of course, essential. The temporary release of the catatonic from his gummed-up condition with the use of carbon dioxide is interesting evidence of the organic nature of this symptom.

In paranoia, the main problem is protection of the public. The problem is usually best handled by prompt hospitalization.

I have experimented with a few cases and have found that the advertised efficacy of sodium rhodonate and sodium amytal is doubtful. The concept that splits cases of mental disorders into two groups is too naïve to merit prolonged discussion. Probably a physical constitution of one type reacts well to one sedative whereas one of a different type reacts better to another sedative.

Purposely, I have omitted in this review mention of psychoanalysis. I believe that psychoanalysis has little if any value in the field of therapy in the psychoses. I cannot find a satisfying answer to the problem of how an extrovert goal can be reached by an introverting technic. Theoretically, the procedure is too subjective to seem reliable to me. Moreover, to me the procedure seems to be backward-looking, toward the paleokinetic, the instinctive, the noninhibited and the emotional, and not forward-looking, toward the neokinetic, the deliberative, the reasoning and the intellectual.

DISCUSSION

DR. H. POWERS: I think that there is a certain modified form of psychoanalysis that has its uses. Sometimes one can find out whether a patient's delusions are secondary to hallucinations. If a patient hears voices and believes them, he may build up a complicated delusional system, in which case I consider the delusions as secondary to the hallucinations. When the delusions are in this sense secondary, I have found it possible to reorient the patient by psychotherapy, and

the results seem to be permanent. This is not possible when the delusions are what I would call primary. I was glad to hear Dr. Gregg use the term dementia praecox instead of the term schizophrenia. I do not think that anything was gained when the word schizophrenia was introduced. It was simply substituting one symptomatic diagnosis for another symptomatic diagnosis, and the symptom is not pathognomonic of dementia praecox, because dissociation occurs in various psychoses.

DR. R. M. KAUFMAN: I am not quite so ready to throw psychoanalysts outdoors in the matter of psychoses. I know of a small group, Zilboorg and others, in America who have obtained results. A man with several college degrees has come to my attention; he has spent the greater part of thirty years in an institution, the last period being of eleven years standing. Under a freudian technic he has changed his point of view. He now makes plans for the future and is grasping out for a readjustment. During the psychoanalytic procedure this man has shown remarkable changes.

DR. F. H. PACKARD: I wish to emphasize the value of an intimate personal relationship with the patient, which Dr. Anthonisen has mentioned.

DR. K. J. TILLOTSON: The type of analysis that most modern psychiatrists use, although it came into being before psychoanalysis, is borrowed from the formal analysis of Freud. As to the use of schizophrenia instead of dementia praecox, if you have a psychopathic member in your own family, would you want to pin on him a label of dementia praecox? Are we justified in saying that a person is going to become demented until after we know he is demented? One should use the term schizophrenia in early psychotic cases but not pin a label on the patient.

DR. I. HENDRICK: I believe that a person is engaging in malpractice if he does not have a medical background. Through medical training and experience, much is learned about the body, but medical training should teach when medical knowledge has reached a limit. A physician who attempts to treat psychiatric problems about which medicine has taught nothing may also be capable of malpractice. There is another point, the care of potentially suicidal patients. This is one of the things in which a more general recognition of certain points would be beneficial to the psychotherapist. Ninety-nine per cent of psychiatrists are petrified at the idea that there may be a suicide in their establishment. Its prevention is their first responsibility, but in fact not to take a certain risk in certain cases under intensive psychotherapy impairs the chance of helping a patient. The surgeon who turned away from every case in which the patient might die on the operating table would miss many chances of saving life. The same is true with psychiatrists. Someone, I think it was Bleuler, expressed this epigrammatically: A psychiatric institution without a few suicides a year is doing very poor work.

DR. N. ANTHONISEN: Patients are brought to institutions to be protected. By so doing their illnesses may be prolonged, but one is fairly sure of saving them. The psychiatrist who has entire confidence in his own judgment of the likelihood of a patient committing suicide is taking a good deal for granted.

DR. D. GREGG: I hope nothing that I have said will be interpreted as meaning that I do not consider personal relationship with the patient of the greatest importance. Study of a case from the point of view of the factors involved is important. What I would avoid is the technic that introverts a patient's attention for months. As regards the suicide situation, I recognize that any person who is determined to take his life can do so regardless of precautions that are taken; the degree to which such precautions are enforced must vary with the case, but one should recognize the danger and not flaunt temptation in the patient's way.

Book Reviews

Die Psychoanalyse. Eine Kritik. By Oswald Bumke. Price, 3.90 marks. Pp. 75. Berlin: Julius Springer, 1931.

Oswald Bumke is a much more cautious and, one might say, generally orthodox and disciplined critic of Freud than many. He singles out the annoying and the weak points of Freud with a more selective judgment and less obvious deviations not only from Freud but also from other organized points of view. He begins with Freud's statement of a sense of futility or impossibility of a sufficient getting together for any discussion with his opponents. Bumke asks for proofs and doubts the status of psychoanalysis as a science. He turns down the dogma and combats the method more than the content of the doctrine. He thinks that Freud materializes what is "psychic." He wonders at the novelist Thomas Mann's evaluation of Freud's libido theory as "romantics turned into natural science," and sees in the whole movement a manifestation of the modern recognition of irrationalism. Bumke finds himself corroborated by Michaelis and Meylan, who analyzed Freud with his own method and raised the accusation that hate and revenge play a great rôle in Freud's teachings. Bumke quotes this partly with approval and partly to show to what preposterous results the method can lead. He looks for contradictions and finds them in Freud's claim that he adheres to psychology and yet has to look to biology for the support of his instinct theory. (Evidently psychology does not belong to biology in Bumke's system.) Freud makes various statements about the unconscious and about consciousness that appear to be flat contradictions. Hence, Freud's psychoanalysis is neither natural science nor any science at all. He quotes at length the account of the libido theory and Scheler's critique thereof, and, further, a fragment from the account of an analysis furnished him by a patient, the claim that the neurotic symptoms are substitutes for sexual satisfactions, the difficulties that arose with the war neuroses, the interpretation of lapses of speech and the continual identification of interpretation and "fact." All this leads to a discussion of the unconscious in Freud's sense — with special reference to Freud's reminiscence of how Bernheim elicited facts buried for a time by hypnotic suggestion, just by insisting and without renewed hypnosis. Bumke accepts the concept of repression in Nietzsche's sense, but refuses to accept more than one consciousness and the censorship and the "necessarily symbolic" nature of dream material, with its supposedly intentional tendency to disguise what cannot be fully repressed. He turns on the symbols and mechanisms, the mythologic analogies and dream interpretations, and the genitalization of the whole body and raises the question of how one can get any proof in a field in which any kind of claim is possible. With regard to a cleverly chosen dream, the reader should realize that Freud would not seek the proof for his interpretations merely in the specific dream, but in the relations to the total development of a person's analysis. It is obvious that Freud excels — and wallows — in trends of associations and relations which are not Bumke's predilections and which are indeed open to the question whether, or at least when, they are preoccupations worth cultivating between physician and patient and as a special sweeping and obligatory system of pathology and therapy. The freudian utilization of the dream and of the Prometheus and Oedipus topics is criticized. Bumke defends himself against the possible reproach of shrinking from the sexual and urinary and other considerations and taboos; "chemistry knows of no dirt"; he wants to be understood as objecting largely to the claiming of things which nobody can refute and which nobody can prove. He objects to Schilder's acceptance of a return to intuition as a second type of logic, and refers to the similar ideology of anthroposophy and Christian science and to the introduction of a new logic, at the same time defending himself and also Husserl against a misunderstanding

by those who see in Jaspers's introduction of phenomenology into psychiatry an identification with Husserl's phenomenology. He wants to keep science apart from philosophy, religion, art and literature and free from the "Hexeneinmaleins" of symbolism. He expresses the highest respect for the attitude to life on the part of anthroposophy (and one might add, also, of Christian science), but also emphasizes the need of distinguishing between what he calls religious and artistic and scientific truths and quotes at length both Hönigswald and Hans Kunz to show the philosophic and intellectual objections.

He quotes Stendahl's "Life of an Odd Character" as a literary example of sensuous love of a little boy for his mother, but balks at the generalization which claims this same tendency in every child, with the corresponding hatred of the other parent and the fear of castration disguised in the dreams as fear of being blinded. Psychoanalysis claims infantile, primitive and fundamentally human tendencies in the unconscious as if this were as certain as that water is a compound of hydrogen and oxygen, ignoring the fact that this lies in a field in which proof or disproof is impossible.

The remaining part of the booklet deals with the question of whether the unconscious can actually be said to be a sphere to which one might have a right to attribute the active dynamic working force assigned to it by psychoanalytic theory. Bumke admits that man will often claim emphatically that he had not been conscious of thought processes, whereas in reality the processes as such or the content may just have been forgotten while the accompanying feelings may have been persistent and effective in influencing consciousness, through the psychology of affects and of imageless thought. The resulting lack of clearness and the probability that one might be dealing with a mere herbartian zero point of consciousness is intelligible, but not the further activity of the thought as thought below this zero point. What Bumke says of hazy thinking on page 68 and of the silence concerning day dreams and the denials of superstitions constitutes much of that which Freud actually works with and gets access to. Bumke calls this a rationalization of the unconscious under the heading of amorality and the like, where he would rather talk of unknown conditions of the brain. He complains that Freud shifts uncritically from physical and biologic to psychic concepts and *vice versa,* and that in reality the pacific interpenetration of German psychiatry with analytic concepts is no proof of the correctness of Freud's psychoanalytic theory. Bumke is willing to assume that Freud's erroneous notions may have been a necessary phase in the evolution of psychology. He compares the freudian movement with the beneficial effect of the floods of the Nile and closes with the admission that no psychology will refrain from trying to comprehend man as a whole, but that this goal is attainable with reasonable certainty only with isolated persons. Since Bleuler admits that he does not really believe in the complete unconsciousness of psychic processes, Bumke ventures to say that actually nothing remains of Freud's doctrine and of the distinctions between the adherents and opponents. Freud's method will disappear, because, if it endured, it would be the end of all science, the end of all research. Somehow the last footnotes to the effect that Adler's "individual psychology" appears more acceptable than Freud's doctrine makes one suspect a "more or less" and not a total nonrecognition of the products of the psychologic talents of a Freud, a Janet and especially of Nietzsche, despite the erroneousness of the method.

Schizophrenia. By Helge Lundholm. Duke University Psychological Monographs, No. 2. Pp. 116. Durham, N. C.: Duke University Press, 1932.

There is no doubt that a great deal of progress in psychiatry is to be expected from the application of psychologic methods and psychologic reasoning to the study of psychopathic patients. This contact between psychology and psychopathology can be effected in various ways. Some psychiatrists are fully trained experimental psychologists and have themselves used psychologic methods on their patients. Then, in recent years, most interesting data and perspectives

have been gained from investigations carried out on psychopathic patients by experimental psychologists without any specific psychiatric training. However, one way in which psychologists have approached psychopathologic problems not only is not conducive to progress, but is harmful and misleading to students of both sciences. The present volume, published as the second of a series of "Duke University Psychological Monographs," is a typical example of the last kind, and illustrates some of the defects characteristic of an unfortunate trend taken by some of the recent psychologic literature. For this reason, a few of its characteristics should be mentioned.

This book purports to give a psychologic theory of schizophrenia. Nevertheless, it is evident to the experienced psychiatrist throughout the whole text that the author (evidently not a physician) has only a most imperfect knowledge of the elementary data of descriptive psychiatry and personality study. Despite this considerable handicap, the author does not hesitate to dispose of psychiatry and psychiatrists in a supercilious manner, and manifests no hesitation in criticizing such masters as Kraepelin, Bleuler and Kretschmer. Many of the statements about psychiatric data and about the views of psychiatrists are incorrect. Thus, he believes that Kraepelin "maintains stoutly" that every case of dementia praecox ends in dementia, and he ridicules the psychiatrists who speak of recovered cases of schizophrenia.

The author claims that in this book he will make no reference to psychoanalytic views of schizophrenia; then he goes on to discuss at some length such definitely psychoanalytic conceptions as sublimation, repression, the reality principle (which he chooses to call "R-function") and rationalization. He "interprets" manic-depressive psychosis as of toxic origin, without giving any concrete data regarding the existence or the nature of such a toxin. He states that in the severest degree of manic-depressive psychosis "the patients are spoken of as confused." He states further that the traditional theory is that the schizophrenic patient is "always of the withdrawing, seclusive type of personality."

What the author expounds are desk-derived, extremely formal conceptions. He speaks of six simple personality traits which he divides into two groups; namely, altrocentric and egocentric traits. His main thesis about the psychology of schizophrenia is the statement that "egotism is the common and obvious feature of the schizophrene, previous to and throughout the psychosis." This fundamental egotism of the schizophrenic patient he contrasts with the essential altruism of the manic-depressive patient. It is an oft-stated observation that this conception, superficial as it is, does not correspond to the actual facts met with in clinical experience. But even if it were correct, it is useless to attempt to understand so complicated a process as schizophrenia when aided only by a few normal psychologic concepts.

Unfortunately, the author is not sufficiently familiar with the concrete methods and data of psychopathology to profit by the criticism of psychiatrists who have had long experience with patients. His comment on a critical expression of Bleuler's about his work is that Bleuler "has not fully understood the situation." He goes so far as to believe naively that the diagnosis of "egotism in young children, and subsequent corrective measures, may prevent schizophrenia." Some of his expressions, e. g., "the classic picture of the displaying paranoiac," are lay expressions the meaning of which is not clear.

This monograph contains no concrete data and no adequate descriptions which would be of use to the psychiatrist or the psychologist. It is written, to borrow the author's term, in an "egotistical" style (e. g., the author points out that he proposes to call the catatonic stupor "pseudo-stupor"; or, elsewhere, he mentions that in the light of his own researches the importance of Kretschmer's conceptions becomes "greatly reduced"). The literature of the subject is only imperfectly considered. The great contribution made by Bleuler to the psychology of schizophrenia is not brought out, and the work of Adolf Meyer and the important modern studies on the psychology of schizophrenia are not mentioned.

Précis de diagnostic neurologique pratique. By J. Lévy-Valensi. Second edition. Pp. 646. Paris: J. B. Baillière et fils, 1932.

In the second edition of his well known Précis, Lévy-Valensi has adhered to the original purpose of the volume: to aid the student and practitioner in making a neurologic diagnosis. "Neurologic diagnosis should answer the three following questions: What is the system damaged? At what level? By what? The first question is a physiologic, the third a biologic, but the second is purely a geometric one." While admitting that the present-day trend is away from the localizing function of the neurologist, he remains faithful to the "classic facts of localization," with some reserves made necessary especially by the work of von Monakow on diaschisis.

The volume is in three parts. The first deals with generalities, the motor and sensory pathways, special levels (reflex, peripheral neuron, vesical, anorectal and genital apparatus) and the visual apparatus. The second part deals with a systematic neurologic examination. The examination of the reflexes is especially complete, with descriptions of some tendon and periosteal reflexes described by Guillain and Barré and by Alajouanine (hamstrings, medioplantar and mediopubien). One misses here mention of those reflexes designed to test the integrity of the cranial reflex arcs by way of the posterior longitudinal bundle, with the exception of the jaw jerk (viz., the nasopalpebral, cochleopalpebral, the palpebral defense reflex and palpebral reflex to light), as well as the postural reflexes. One cannot agree that "every inequality of reflexes, every evident modification of the reflexes, is a sign of a nervous system lesion" (p. 33). In the second part too much space is given to a description of the Wassermann reaction.

The third portion of the volume is a description of neurologic and endocrinopathic syndromes: comas, hemiplegias, paraplegias, states of generalized hypertonus, cerebellar and vestibular syndromes, tabes, amyotrophies and myopathies, poliomyelitis and polioencephalitis, aphasias, apraxias, epilepsies, tremors, choreas, spasms, intracranial hypertension, radicular troubles, paralyses of the spinal nerves and of the cranial nerves, neuralgias, hysterical states, dementia paralytica, the sympathetic system and syndromes of the endocrine glands. The chapter dealing with paraplegias gives the differential points between the spastic and the flaccid varieties, including paraplegia in flexion of cerebral origin (Alajouanine). The chapter dealing with spinal nerve paralyses is especially complete. In the discussion of hypertonic states, one misses mention of the Kayser-Fleischer corneal ring in the differential diagnosis of hepatolenticular degeneration. In the chapter dealing with intracranial hypertension is mentioned the use of the tonometer of Bailliart, which is too much neglected in American practice. There are excellent chapter summaries in the form of tables of differential diagnostic importance.

The new edition gives space to the reflexes already mentioned, to tumors of the brain, medullary compressions, the autonomic nervous system and to oculogyric crises of encephalitic origin. Lévy-Valensi has purposely and rightly omitted from the volume mention of the psychoneuroses, except hysteria, which encroaches by "simulation" on the neurologists' domain. Among the psychoses, dementia paralytica alone is mentioned, with too summary an indication of the psychiatric diagnostic points. There are occasional statements which may well be challenged, as, for instance: "The reflex (tono-dynamique) will be abolished in case of diffuse cerebral lesions (dementia paralytica, dementia praecox)" (p. 73).

The volume is profusely illustrated, largely with K. Wagner's drawings and schematizations, many of which present in a striking fashion points of diagnostic importance. On the other hand, many of the photographs from life are unconvincing. The volume is an excellent example of French neurologic teaching, which is pictorial to the highest degree. It shows the French flair for the needless multiplication and subdivision of syndromes, and in its totality presents an assortment of disease pictures well nigh staggering to any but the French student. As with most French textbooks, this volume suffers from the lack of a good alphabetical index.

Les abcès cérébraux et leur traitement. By Jean Piquet. Price, 22 francs. Pp. 151. Paris: Masson & Cie, 1931.

This is an excellent little thesis on the subject of abscess of the brain. The reviewer agrees with the author in his premise that abscess of the brain always follows infection of the bone, and, therefore, that this condition is a sequela of chronic otitis media and not of acute otitis media. He states that in those cases of abscess of the brain in which the lesion apparently occurs following acute otitis media, the apparently acute disease of the middle ear is almost certainly an exacerbation of a preexisting chronic disease of the middle ear. Piquet believes that if infection follows an acute otitis media the infection is probably so virulent that it passes rapidly through the bone and infects the subarachnoid space producing a meningitis, because there has been no chance for adhesions to occur between the meninges and the cortex, which is always the case in a slowly developing chronic condition.

As regards the way in which an abscess is formed, Piquet believes that the infection passes slowly through the bone, gradually involves the meninges, causing adhesions between the meninges and the surface of the brain, and then passes inward either by direct extension or by septic emboli entering the adjacent vessels.

Piquet further emphasizes the fact, which I believe to be very important, that it is well nigh useless to operate on an unencapsulated abscess of the brain. If drainage is instituted during the period of acute cerebritis, before the defense mechanism of the brain has had an opportunity to localize the infection, no drainage results and the trauma of introducing the drain helps materially in handicapping the efforts of the brain in localizing the lesion. He believes, therefore, that if success is to follow a surgical attempt to evacuate an abscess, sufficient time must be permitted for encapsulation to occur. He believes that a solitary encapsulated abscess, if properly treated with a minimum of trauma to the brain during the introduction of drainage, gives a fairly good prognosis. Multiple metastatic abscesses or posttraumatic abscesses present a much less favorable outcome.

Piquet considers the point at which drainage is to be instituted important. He takes the stand that the abscess is always in close relationship to the infected bone and that the best area through which drainage can be instituted is through the diseased bone. By draining through the region of chronic osteomyelitis two purposes are accomplished: (1) the focus of infection in the bone is eradicated, and (2) a drainage tract is made through an area where adhesions have walled off the subarachnoid space. He believes that soft tubular drainage is the best. Under certain conditions, however, when one is not entirely convinced that an abscess is present, he deems it proper to plunge for abscess through a sterile field adjacent to the point at which the abscess is suspected.

This monograph would be definitely improved if results following these methods of treatment were published. The bibliography is inadequate. It is curious that only a cursory reference is made to the work of Sir William Macewan. The recent publications by Coleman in this country are entirely ignored. On the whole, however, it is a satisfactory thesis, and gives a well reasoned and conservative outline of the manner of development, symptomatology and treatment of abscess of the brain.

La neurotomie rétro-gassérienne partielle dans le traitement de la névralgie faciale (étude anatomique—résultats cliniques). By André Sicard. Price, 35 francs. Pp. 227. Paris: Louis Arnette, 1931.

Sicard has reviewed briefly but thoroughly the anatomy of the sensory and motor roots of the trigeminal nerve. The indications for section of the sensory root and the methods employed are outlined.

After a short description of the clinical material on which the conclusions are based, Sicard reviews the history of the operative procedures used to section the sensory root. Beginning with the removal of the gasserian ganglion as originally

suggested by Krause and Hartley, in 1894, the methods of sectioning the fifth nerve are described. Spiller and Frazier's retrogasserian section of the sensory root through the temporal fossa is outlined, followed by Frazier's two modifications of his technic—to save the motor root and to leave behind the inner fibers supplying the ophthalmic division, thereby preventing keratitis in the ipsolateral eye. Finally, Dandy's subtentorial approach and subtotal section of the sensory root in the posterior fossa are reviewed. Curiously, the suggestion of Hutchinson that a subtotal resection of the ganglion be made, thereby preserving the fibers to the ophthalmic division and preventing keratitis, is completely ignored in the history of the surgery of the trigeminal nerve.

Careful anatomic study of the sensory root showed Sicard that the fibers interdigitate as they approach the ganglion. Fibers were found connecting the motor and sensory roots, raising the interesting question as to whether the motor root may not contain sensory fibers. Because of these findings it is difficult to explain why section of a certain area of the root behind the ganglion always produces sensory loss in relatively the same area of skin. Sicard endorses completely the subtotal section of the sensory root because it prevents keratitis and reduces the area of complete anesthesia of the face. He has never seen a recurrence of the pain typical of tic douloureux following subtotal resection. The temporal approach to the root is in his opinion an easier and less hazardous operative procedure than the subtentorial route.

This is an interesting and valuable little monograph. The author is to be congratulated on the clear and concise manner in which he presents his facts and the conclusions he draws from them.

Selected Writings of John Hughlings Jackson. Volume 2. Evolution and Dissolution of the Nervous System, Speech, Various Papers, Addresses and Lectures. Edited for the Guarantors of "Brain" by James Taylor, M.D., with the advice and assistance of Gordon Holmes, M.D., and F. M. R. Walshe, M.D. Price, 25 shillings. Pp. 510. London: Hodder & Stoughton, Ltd., 1932.

The papers in the second volume of selections from the writing of Hughlings Jackson have been arranged in three sections, the first dealing with the papers on "Evolution and Dissolution of the Nervous System," the second, "Affections of Speech," and the third, "Various Papers, Addresses and Lectures."

Perhaps nothing that Jackson has written from the philosophical standpoint compares with the contents of the lectures on the evolution and dissolution of the nervous system, and in them is contained the broad philosophy of localization and symptomatology.

Jackson's views on speech have been very well brought out by Henry Head in his work on aphasia. The subjects of the various papers, addresses and lectures again indicate Jackson's broader conception of the philosophy of neurology, for he rarely reports a case. A case was used merely to emphasize a conception of the philosophy of the subject. Therein lies Hughlings Jackson's greatness.

Every neurologist as well as every psychiatrist not only should possess these two volumes, but should know their contents. The future of neurology and psychiatry would indeed be golden were this the case.

It is a justifiable tribute to the greatness of Hughlings Jackson that the second International Neurological Congress is to be held in London in 1935 on the centennial anniversary of his birth.

Genius and Creative Intelligence. By Nathaniel David Mttron Hirsch, Ph.D. Price, $4.50. Pp. 339. Cambridge, Mass.: Sci-Art Publishers, 1931.

Dr. Hirsch, onetime Fellow of the National Research Council and recently associate of Professor McDougall in the departments of psychology at Harvard and at Duke universities, is known for his previous works, which include "A Study of Natio-Racial Mental Differences," "An Experimental Study of the East

Kentucky Mountaineers," "Twins; Heredity and Environment" and "An Experimental Study of Three Hundred Children over a Six Year Period." At present he is chief psychologist and research director of the Wayne County Clinic for Child Study.

This book is a careful and comprehensive survey of the occurrence and phenomena of genius considered from many points of view in an objective manner. Dr. Hirsch adopts the point of view of almost a pure biologist and uses as his standard the concrete criteria of mental testing and anthropologic research wherever this is possible. Yet he also makes the survey in the light of modernly conceived psychologic mechanisms and considers the dynamics of intelligence in a painstaking and understanding way. The influence of the author's knowledge of psychoanalytical and Gestalt writings is seen in this book, and this fact, as merely one among many, makes it different from previous books dealing with the complicated subjects of creative intelligence and genius. The style of this book is not popular, as it is too thoughtful for the mind that buys its science at corner drugstores, but physicians interested in neurology and psychiatry will find in it a text much more interesting than the ones they usually read and will find the references valuable for further study if they should wish to follow them. The main divisions of the book are three: part 1 "History, Creative Adaptation, and Genius"; part 2, "The Psychological Constitution of Man"; part 3, "An Inquiry Concerning the Nature of Genius." A thorough index closes the volume.

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